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ABLATION OF ABNORMAL CORTEX IN CEREBRAL PALSY*

BY

WILDER PENFIELD

From the Department of Neurology and Neurosurgery, McGill University, and the Montreal Neurological Institute

Cerebral palsy may be defined, in a broad sense, as loss of function due to brain injury. Such injury may affect motor centres producing spastic paralysis of an arm or leg, but it may also affect other areas of the brain and thus cripple other functions than those of movement of the arm and leg.

Hemispherectomy has been proposed recently as a method of treatment of infantile hemiplegia by Krynauw (1950) followed by Cairns (1951). The claim made is (1) that cerebral seizures may be stopped, (2) the mental state improved, and (3) motor function facilitated because of a lessening of spasticity in the paretic limbs. In the 12 cases of severe hemiplegia reported by Krynauw this very radical procedure was apparently well justified. The question to be decided is whether less radical ablations may not be preferable. The results reported for these hemispherectomies illustrate the truth of the thesis, to which I have subscribed for some time, that abnormal cortex, incapable of useful service, does, in some cases, exert a noxious influence upon the rest of the brain which might otherwise function normally Let us examine this thesis under the headings of epilepsy, mental retardation, and spasticity.

Epilepsy

For some years we have been in the habit of excising abnormal cerebral cortex in the treatment of focal epilepsy. To obtain good results wide excision is often necessary but in the great majority of cases there is normal as well as abnormal cortex in that hemisphere. It seems reasonable that the bad should be sacrificed and the good spared for future useful function.

In the treatment of epilepsy, periods of five to 10 years should be allowed to elapse before a summary and conclusion is made of a series of adequate size. We have in the past made three follow-up studies of the results of surgical ablation of focal atrophic epileptogenic lesions of the cortex in the years ending 1939, 1944, and 1950, in a total of 234 patients.

The first study, which was carried out with Theodore Erickson, included all cases of this type operated upon at the Montreal Neurological Institute between 1929 and 1939 (115 patients). They were followed up from one to 11 years. In this series 43% were placed in the success group, which means that each case either had no post-operative attacks, or had one or two attacks before epilepsy ceased. The second study, carried out with Harry Steelman, covered the period 1939–44 (Penfield and Steelman, 1947) with a follow-up period of one to seven years in 59 cases of cortical excision with an operative mortality of 1·2%. Of these, 55·8% were placed in the success group: that is to say, about half of this group had had no attacks after operation and the other half had two or three attacks before cessation.

The third report, carried out in 1950 with Herman Flanigin, consisted in a follow-up of 60 cases of radical operation for temporal lobe epilepsy (psychomotor epilepsy of Gibbs and Lennox). The results were about the same, 55% of undoubted success.

Most of the patients in each series were adults, but it may be pointed out that of the 59 cases reported in the second series, 17 patients were suffering from seizures produced by an unquestioned birth injury and the attacks usually began in childhood. (In many other cases birth compression was a possible cause of the lesions found.) The incidence of success as the result of operation rose in these 17 cases from the general average of 56% to 76%. Thus it may be seen that birth injury provided us with our most favourable group. A single example is given below.

Case 1.—M. M. was referred by Dr. A. Jimenez, Bogota. This little girl, aged 7 years, had received a severe brain injury at birth. She had left hemiparesis and hyperactive deep reflexes and plantar extensor response on the left side. There was marked loss of cortical discriminatory sensibility on the left and smallness of the left arm, leg, and trunk. Her disability in arm and leg was not as great as might be expected from complete destruction of the motor cortex.

* Read before the American Academy for Cerebral Palsy, Boston, on November 16, 1951.

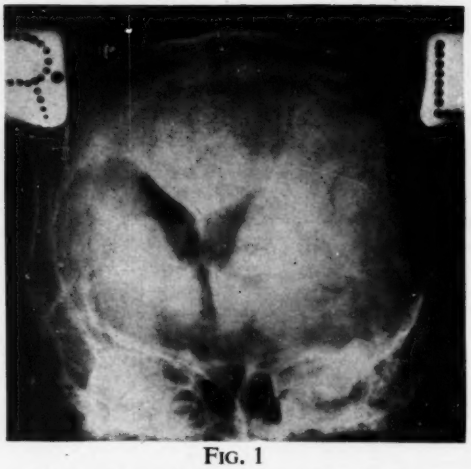

FIG. 1

FIG. 1.—Pneumoencephalogram (Case 1) shows the right cranial chamber to be small and the total volume of the right hemisphere to be very much smaller than the left.

FIG. 2.—Cortical destruction in right hemisphere in Case 1. Note subdural adhesions, also small gyri at periphery of lesion seen dimly through the thickened arachnoid membrane.

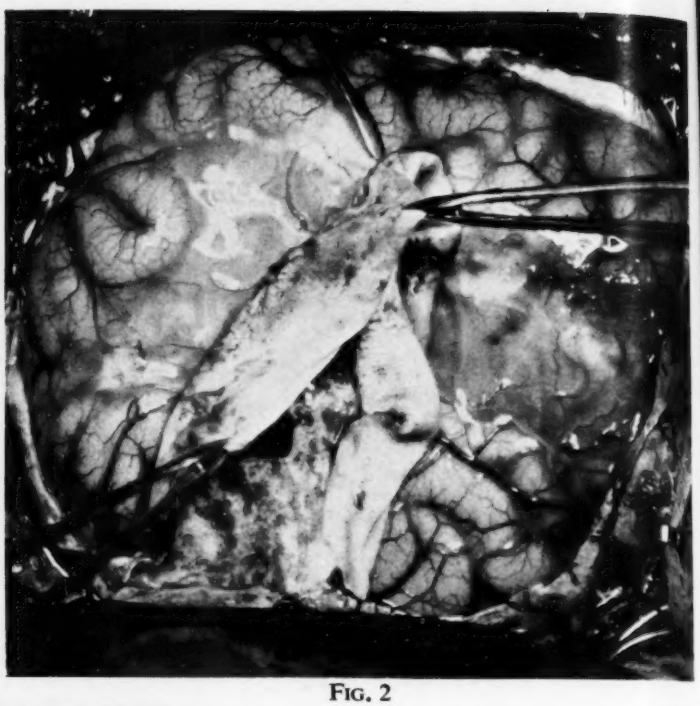

FIG. 2

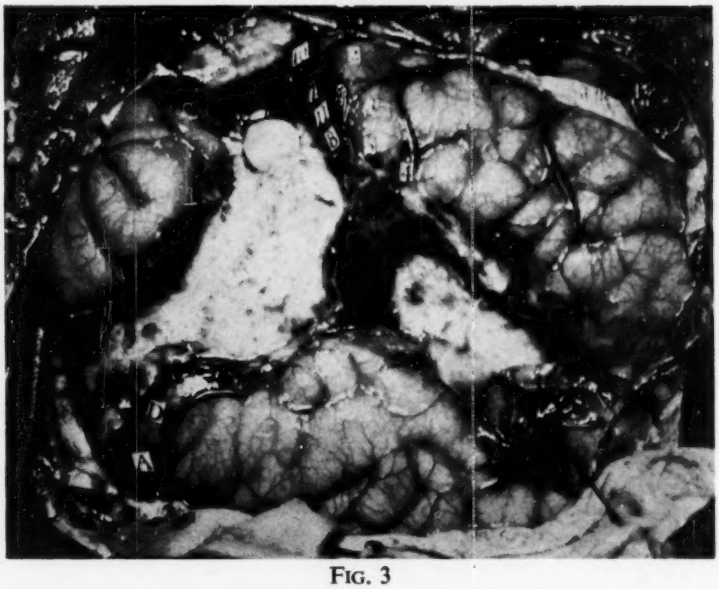

FIG. 3

FIG. 3.—Abnormal tissue (Case 1) and abnormal gyri have been removed by suction down to the white matter that covers the ependyma. Above, the excision follows the fissure of Rolando. Note the normal width of remaining gyri.

Operation under nupercaine analgesia: intravenous pentothal was used to induce sleep during the opening. Child awake and cooperative during cortical stimulation and electrocorticography. Stimulation at 2, 3, 7, 10, and 11 produced movement of left leg; at 5 flexion of elbow; at 4 apposition of thumb and finger. A and D indicate sharp wave E.E.G. focus which disappeared following the ablation.

Cerebral seizures had begun at the age of 4½. She had been well behaved and intelligent, but during the year before operation her mother was of the opinion that she had been "slowing down".

Pneumoencephalography showed marked smallness of the right hemisphere (Fig. 1). At the time of right osteoplastic craniotomy there was a central area of brain destruction surrounded by a peripheral zone of shrivelled gyri (Fig. 2).

Electrocorticography demonstrated a focus of spike discharges in some of these gyri located in the post-central region. After careful excision of all abnormal gyri down to the wall of the ventricle (Fig. 3) the remaining cortex appeared normal. The spike discharges were gone, and it is of interest that with them a sharp wave E.E.G. focus that had been present in the temporal lobe (at A and D, Fig. 3) also disappeared.

This case illustrates the fact that a small hemisphere may contain normal cortex and abnormal cortex as well as areas of complete destruction. The removal involved parts of the parietal, temporal, and frontal lobes but spared the arm and leg area of the precentral gyrus, as is shown in Fig. 3.

The little girl has had no increase in hemiparesis and no seizures in the year that has followed operation.

Mental Retardation

When abnormal brain is removed in the treatment of cerebral seizures there results, not infrequently, a marked improvement in mental capacity and behaviour. This is usually true when the attacks have been successfully stopped or greatly reduced. Of course the psychological effect of freedom from seizures may be a factor in this improvement, a factor which applies to adults but hardly to children. The decrease in the amount of anticonvulsant drugs may also be a feature, but phenobarbital alone is invariably continued during the first few post-operative years.

Progressive mental retardation is a prominent feature of some cases and is absent in others, even though seizures may be frequent in both. This would suggest that the abnormal area of brain exerts a noxious influence upon normal areas even in the absence of overt seizures.

A study of the effect of removal of abnormal brain was carried out by Hebb and Penfield (1940). Extensive removal of both anterior frontal lobes was carried out in a young man to stop seizures. The primary objective was only partially achieved, as he had two seizures in the subsequent 15 months.

Professor Donald Hebb carried out exhaustive psychological studies and concluded that, even though about one-third or more of each frontal lobe was missing after operation, " there was a striking post-operative improvement in personality and intellectual capacity with the same medication as before operation ".

The conclusion was *not* that a normal individual with normal brain may be improved by cortical ablation, but that " abnormal areas of brain may produce, in a positive sense, both decreased mental capacity and abnormalities of behaviour, and that the absence of these areas may allow other parts of the brain to recover their normal functions ".

Electroencephalography also gives evidence that in such cases partly destroyed cortex exerts an influence on otherwise normal areas of the brain. Diffuse abnormality of electrical potentials may appear in both hemispheres after a period of time, especially in the case of those patients who are said to be clinically retrogressing. Dr. Herbert Jasper has concluded from post-operative study of numerous cases in our clinic that diffuse and continuous E.E.G. abnormality sometimes disappears or may be greatly reduced after successful ablation of a focal epileptogenic area of cortex in one hemisphere. This is seen most often in children.

There are young children and infants who have received brain damage due to ischaemia or trauma at birth, but who seem to do well for a period. Then cerebral seizures appear and their intelligence fails or development is arrested. There are such patients who become increasingly hemiplegic as the attacks continue. Every clinician of any experience must have seen this sad retrogression more than once. For lack of better explanation he may make a presumptive diagnosis of chronic encephalitis or degenerative disease of the brain.

The patient reported below was studied over an eight-year period and reported by Penfield and Livingston (1949).

Case 2.—The birth of H. F. was not considered unusual. On the second day of life, however, he vomited and had two short convulsions. The spinal fluid contained blood. From the fifth day onward, he seemed normal, held up his head at 3 weeks, sat alone at 4 months, and appeared to have normal intelligence.

At 5 months he had a left-sided convulsion, and similar attacks followed with increasing frequency despite medication. At 1 year he was unable to sit up and seemed completely disassociated from his surroundings.

An electroencephalogram showed marked abnormality on both sides (Fig. 4a) with epileptogenic activity on the right. Operation was carried out on the right, and cortex that had been partly destroyed by natal intracerebral haemorrhage was removed. Six weeks later the E.E.G. was normal as shown in Fig. 4B. At 8 years of age the boy was free of attacks. He was in the second grade at school and had a mental age of 6 years and 2 months which was far better than anything that could have been hoped for at 12 months without operation.

" Nociferous " Cortex

Let us consider the case of any patient who has a brain lesion and is destined to develop epileptic seizures. In the period between the reception of brain damage and the onset of seizures, it is obvious that a gradual alteration occurs in injured grey matter. This interstitial or cellular alteration eventually results in seizures years, perhaps, after the lesion was established.

The nature of the change in the damaged area of grey matter is not clear. But Pope, Morris, Jasper, Elliot, and Penfield (1947) have demonstrated elevated cholinesterase content in such foci, and Tower and Elliot (1952) have shown that there is a local decrease in the capacity to combine acetylcholine. The electroencephalogram suggests that this is associated with increased spontaneous liberation of energy in the area.

It would appear then that that focus of epileptogenic activity may interfere with the function and

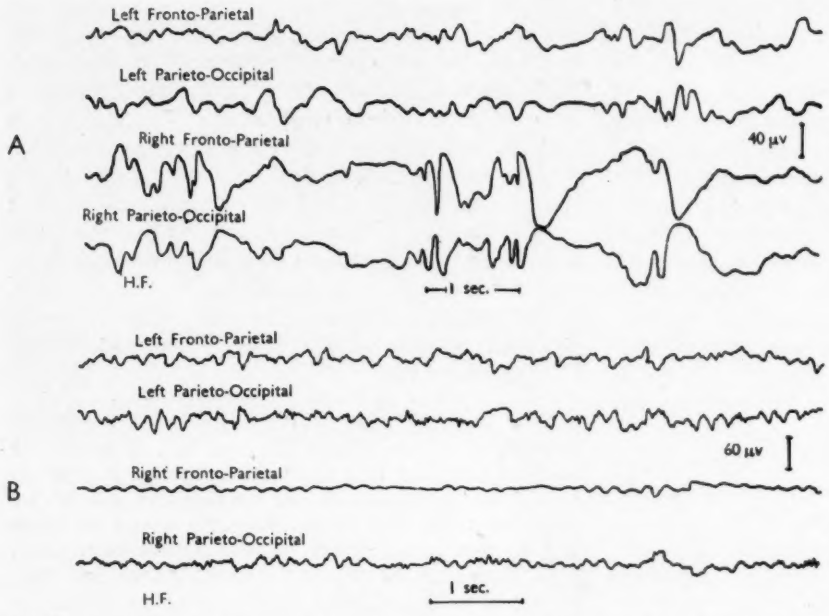

FIG. 4.—Electroencephalograms of Case 2.

A. Before operation: note random delta and sharp waves arising from all head regions, with phase reversal of spikes, sharp waves and random delta waves occurring midway between right ear and vertex.

B. Six weeks after ablation of epileptogenic area of cortex in right frontal lobe near falx. This record shows only a background rhythm at a frequency of 4 to 5 per second. This should be considered normal for a child of this age. (Interpretation by Professor Herbert Jasper.)

the evolution of the uninjured portions of the brain. What begins as a local affair ends with generalized abnormality. Such an area of cortex must be considered as a source of noxious influences, a concept which might be described by the somewhat obsolete adjective " nociferous ".

When such a train of events is established in infancy and the child arrives at years which should be years of understanding, there may be little left to save. Operative procedures are better controlled and less subject to risk at 10 years of age than at 2, but we have been forced to reconsider our policy of postponement in regard to radical ablation of epileptogenic cortex in those cases in which there is evidence of progressive intellectual degeneration or progressive paralysis.

Does mental retardation always develop in patients who have recurring seizures due to a cortical lesion? Patients often ask this question. The answer must be, " No, by no means." In some there is intellectual deterioration; in others there seems to be little or none. But when such change begins, the outlook for the future is ominous.

In regard to localization it may be said that temporal lobe seizures are most often associated with progressive intellectual and behavioural abnormality in adults. Among infants and children no particular localization has been apparent. The number of overt seizures is often no index of whether or not a lesion of the brain is exerting a noxious influence upon its general performance.

At times very large excisions are necessary when the area of partly destroyed cortex is large and when electrographic abnormality is widespread. Such a situation may be illustrated by the following:

Case 3: K. M.—The extent of removal which seemed necessary is shown by the broken line in Fig. 5. Fig. 6 shows that the posterior half of the right hemisphere has been removed and that the remaining cortex is comparatively normal. The ventricle is about to be closed.

Motor Function

We have gradually come to realize that sufferers from severe hemiplegia are sometimes benefited by complete ablation of the abnormal Rolandic sensori-motor cortex. This apparent paradox is to be explained by the fact that a lesion of one hemisphere may render the motor cortex useless and yet not destroy it. Under such circumstances removal of the cortex may result in a decrease of spasticity (Welch and Penfield, 1950).*

In order to understand this, it must be realized that ablation of the precentral motor gyrus of a normal individual does not produce complete paralysis. It produces initial paralysis which is soon replaced by paresis more marked in the arm than in the leg. Such an individual can walk and he can use his arm and hand for gross movements. Skilled movements of the fingers and movements of individual toes are lost forever. Thus a patient, who already has no control of the hand for delicate movements, has little to fear as the result of excision of the arm area, and it is possible that the arm may

* It may also result in cessation of Jacksonian seizures, supposing, of course, that the patient had complained of seizures.

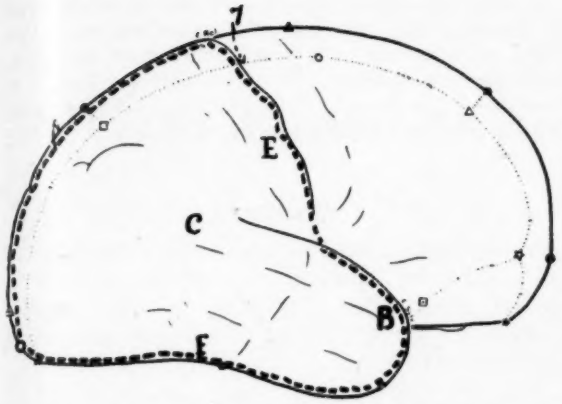

FIG. 5.—The extent of cortex removed in Case 3 is indicated by the broken line, and the extent of electrocorticographic abnormality by letters E, C, F, and B. Metrazol was given intravenously during operation to increase the abnormal potentials.

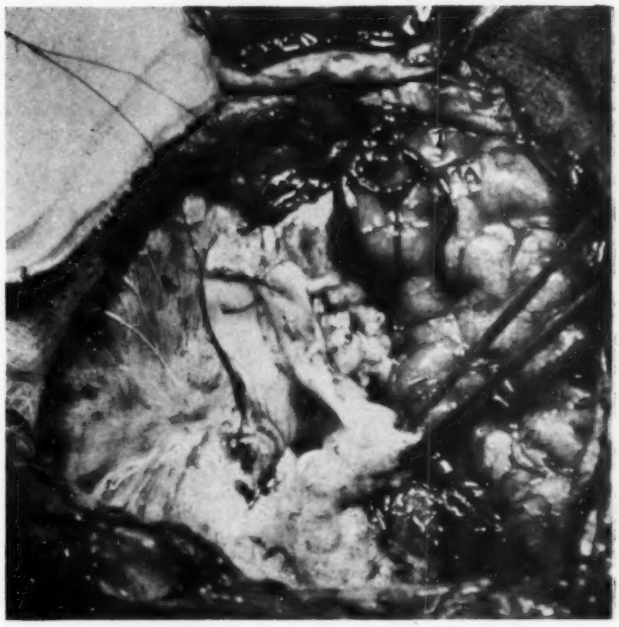

FIG. 6.—Occipital, parietal, and temporal lobes have been removed in Case 3. Stimulation at 7 produced movement of left leg. The ventricle is open but enough of the ependyma has been left intact so that it can be closed by silk sutures, the first of which is shown. This closure avoids post-operative elevation of temperature (" aseptic meningitis ").

thus be freed of a good deal of the spasticity that hampers those movements of which he is otherwise capable.

After the motor cortex is excised movement seems to be controlled by subcortical mechanisms (Penfield and Rasmussen, 1950). A lesion deep in one hemisphere results in a much more severe paralysis than that produced by cortical excision.

On the other hand there are many cases of cerebral palsy in which ablation of motor cortex will convert hemiparesis into a more severe disability. In such cases, unless the motor gyrus serves as epileptogenic focus, it is preferable to spare this area of cortex.

One more case may be cited very briefly, that of a baby who was treated with very radical operation. It is possible that Mr. Krynauw would have recommended hemispherectomy. The result is encouraging so far, but only time and a great deal more experience will make it clear how radical the neurosurgeon should be.

Case 5.—F. S. was referred by Dr. Henri Gastaut, Marseilles. Birth was difficult and the child was cyanosed. On the second day of life there were convulsive attacks involving the right arm. At 5 months right-sided seizures appeared. At this time the parents believe the child to have been normal mentally. He ate well, played games such as " patty cake ", and handled toys normally.

From 5 months on there was steady retrogression and at $2\frac{1}{2}$ years, when operation was undertaken, the child was grossly retarded, did not play with toys and was unable to stand or walk alone.

At that period, E.E.G. examinations by Professor Gastaut showed " spikes " and also sharp wave abnor-

FIG. 7.—Operative exposure of the left hemisphere in Case 5. As the dura was reflected adhesions to the pia had to be cut. Beneath the adhesions the gyri were narrow and indurated. Anteriorly and posteriorly they appeared normal.

malities from both hemispheres, although earlier electroencephalograms had shown only a focus in the left hemisphere with normal activity on the right.

The boy had a right hemiparesis and a small right arm and leg. Radiographs showed comparative smallness of the left cranium. The ventricles were somewhat large, the left being larger than the right, particularly in the central region (portions 2 and 3).

A large left-sided osteoplastic craniotomy was carried out. This disclosed a remarkable zone of small gyri in the central region, some being as narrow as 2 or 3 mm. Over this area the dura was adherent, as shown in Fig. 7. In the frontal and occipital regions there was a gradual change to gyri of relatively normal appearance (Fig. 7).

A wide excision was carried out and this was then enlarged further because Dr. Jasper reported continuing electrocorticographic abnormalities on the frontiers. The final removal is shown in Fig. 8.

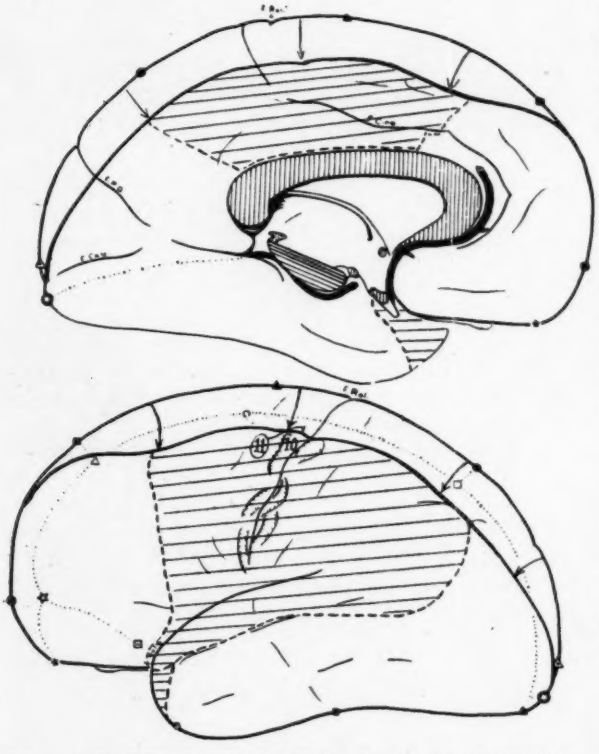

FIG. 8.—The extent of cortical ablation in Case 5 is indicated by the shaded area. It was necessary to include the whole of the first temporal convolution down to and including the uncus. Stimulation at point 10 produced arm movement and at 11 movement of foot.

The smallness of the left hemisphere compared with its expected size is indicated by the arrows to the inner outline.

A year after operation the child had apparently had no seizures. The electroencephalogram was very much better. He used his leg better than before operation, although it was weak. The right arm was carried in flexion. There was "magnificent" psychological improvement and he spoke in monosyllables.

Summary

In conclusion, patients who suffer from cerebral palsy may be benefited by cortical excision in various ways. But they must be very carefully studied and selected before such radical procedures are to be considered.

The possible benefits may be reviewed as follows. (1) The patient who is subject to recurring cerebral seizures may be relieved of his attacks. (2) The patient who has a discharging lesion of the cortex and shows progressive mental retardation may be greatly improved by excision of the partially destroyed cortex provided that the intellectual degradation has not gone too far. This applies particularly to children in the early stages of mental retardation and behaviour abnormality. (3) Patients suffering from severe hemiplegia from infancy may be freed from spasticity to a considerable extent by cortical motor excision.

In our experience, complete hemispherectomy would rarely be advisable. But subtotal hemispherectomy and the discriminating ablation of all nociferous cortex is a form of therapy that can bring great improvement to selected sufferers from cerebral palsy.

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J. Neurol. Neurosurg. Psychiat., 1952, **15**, 79.

THE EFFERENT FIBRES OF THE HIPPOCAMPUS IN THE MONKEY

BY

D. A. SIMPSON

From the Department of Human Anatomy, University of Oxford

Speculations upon the functions of the hippocampus have been numerous in the last few years and have led to some important experimental studies. In the critical review by Brodal (1947) the obscurity surrounding the afferent connexions of the hippocampal complex was stressed. Since the publication of this paper, the hippocampal afferents from the cingulate cortex have been examined experimentally in the rabbit (Adey, 1951) and in the monkey (Adey and Meyer, 1952) by Glees' silver method, and Pribram, Lennox, and Dunsmore (1950) have presented electro-neuronographic experiments on the connexions of the entorhinal and prepiriform areas in the macaque.

The efferent projection of the hippocampus has been the subject of some recent experimental studies, notably those of Sprague and Meyer (1950) on the rabbit, employing the Glees method, and of Allen (1944, 1948) upon the dog, using both the Marchi technique and the examination of early retrograde changes. These experimental investigations were made on lower mammals, and earlier workers (von Gudden, 1881; Probst, 1901; Edinger and Wallenberg, 1902; Yamagata, 1927; Le Gros Clark, 1932; Gerebtzoff, 1941–42; Fox, 1943; Allen, 1944) have also used rodents and carnivores (vide infra). The Dejerines (1897), indeed, briefly describe the fornix fibre degeneration in a human brain in which the hippocampus, the splenium, and other structures had been destroyed by cerebral softening. Their technical methods, however, are not adequately described; moreover, their lesion appears to have been so massive as to make some of their conclusions unreliable. Since the allocortical structures are by no means constant phylogenetically, it seems important to confirm in the primate brain the observations made on subprimates, and to employ methods giving more precise information than is obtainable by the Marchi method used by most of the authors quoted. The experiments reported here were designed to provide accurate knowledge of the termination of the efferent fibres of the hippocampus in the monkey. The findings of previous workers have also been reviewed in some detail, for they appear to demonstrate significant phylogenetic variations in the destiny of these fibres.

Material

Numerical Examination of Fornix Fibres.—As a preliminary to a detailed investigation of the destiny of the fornix fibres, an attempt was made to estimate what proportion of these fibres reach the mamillary body. An approximate indication of this may be obtained by counting and comparing the number of fibres in the fornix before and after the departure of its precommissural component.

Selected portions of the fornix of a young, healthy macaque were embedded in paraffin wax, cut transversely at 5μ, and stained with Bodian's protargol. Two levels were examined quantitatively: the fornix beneath the corpus callosum, just behind the caudal extremity of the septum lucidum, and the descending column of the fornix in the hypothalamus (Fig. 1a, 1b). In the first, the precommissural fibres are included, while at the latter level, these have presumably left the main bundle. At each level fibres in 10 areas chosen at random were counted, using the camera lucida method recommended by Allison and Chacko (1949), and the total cross-sectional area of the fornix at the two levels was estimated both from photographs and from tracings made with the camera lucida on squared paper. In the sub-callosal part of the fornix, the average fibre density was 48 fibres per 100μ^2; in the hypothalamus the density was greater, 74 fibres per 100μ^2. The total cross-sectional area of the two fornix columns together, ventral to the corpus callosum, was 2,220,000μ^2, both methods giving approximately similar figures. At the hypothalamic level only one fornix column was examined; its cross-sectional area was estimated to be 117,000μ^2 by the camera lucida mensuration, and 147,000μ^2 by the photographic technique. It is therefore estimated that each fornix column contains about 500,000 fibres before it enters the septum lucidum, and is reduced to not more than 110,000 fibres in the hypothalamus. The possible sources of error in this initial quantitative analysis are considerable, and more material is needed for confirmation of the results. The counts of fibre density were particularly difficult. However, these figures suggest that the precommissural component of the fornix is larger than the post-commissural, perhaps in a proportion as high as three or four to one.

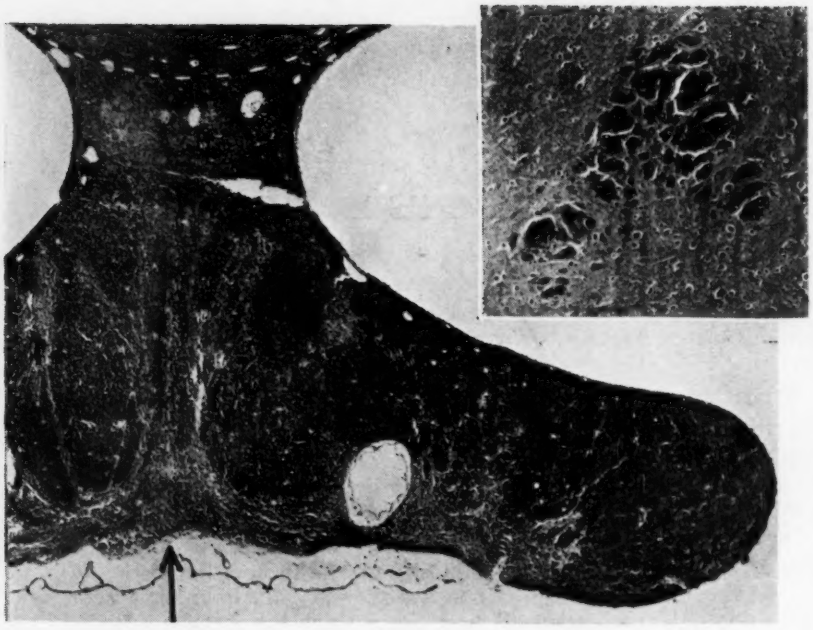


FIG. 1a.—Transverse section of the fornix column in the roof of the third ventricle immediately behind the caudal extremity of the septum. The arrow indicates the median line between the two columns. The line of contact between the fornix column and the corpus callosum is marked by an interrupted line. Bodian stain × 40.

FIG. 1b (inset).—Transverse section of the descending column of the fornix of the same brain, immediately above the mamillary body. Bodian stain × 40. Note the marked contrast in cross-sectional area between the fornix in the roof of the third ventricle and the descending column.

Fibre Degeneration after Lesions in Fornix or Hippocampus.—The brains of seven monkeys have been examined. In three (Experiments 1, 5, and 7) lesions were made in the hippocampus of one side, and in four (Experiments 2, 3, 4, and 6) the subcallosal fornices were injured to varying extents. Additional information has been obtained from three brains in which ablations in the region of the temporal pole had been made by Adey and Meyer in a study (to be published) of its connexions.

The degeneration consequent on these lesions was studied with the ammoniacal silver method of Glees, slightly modified in this laboratory by M. Meyer (Adey and Meyer, in the press). Sections were usually cut with the freezing microtome at a thickness of 12 to 15μ. It is well recognized that the evidences of degeneration provided by this method are liable to misinterpretation. In the present report fibres, whether pericellular and presumably terminal or preterminal, or grouped in tracts, are considered to be degenerating only when they are swollen and broken into beads or droplets (Figs. 2 and 3): variations in calibre without actual fragmentation have been disregarded. As occasional degenerating fibres are sometimes (though in the writer's experience rarely) seen in normal material, no deductions have been made from solitary fibres. Boutons terminaux have been accepted as evidence of terminal degeneration only when swollen and present in abnormally large numbers (e.g. in Fig. 4), for it is recognized (Meyer and Meyer, 1945; Glees, 1946) that isolated normal boutons terminaux are occasionally made visible by the Glees and similar methods. Wherever possible unaffected regions were examined as controls of the success of the staining, which is somewhat capricious, at least in the writer's hands. Adjacent sections stained by the methods of Weil and Nissl were employed to give accurate identification of tracts or nuclei studied with the silver technique.

The lesions were produced with the usual neurosurgical precautions. Their precise extent was determined in various ways; frozen sections were much less satisfactory for this purpose than serial sections of material embedded in low viscosity nitrocellulose, which, unlike paraffin wax, permits the use of the ammoniacal silver method.

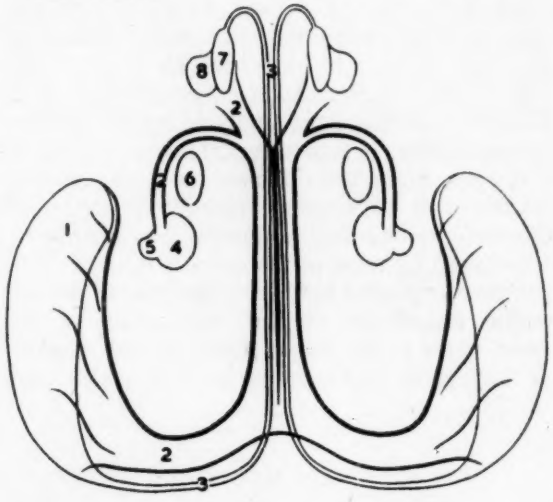
Systematic behavioural and physiological studies were not made, as the survival times of the animals were necessarily brief. However, a few incidental observations of this kind are recorded.

The nomenclature of hypothalamic nuclei is that recommended by Rioch, Wislocki, and O'Leary (1940).

Fig. 5 illustrates schematically the fornix cyst.

FIG. 5.—Schematic representation of fornix system as seen from above; the diagram is numbered as a key to the subsequent figures. 1 = *hippocampus and dentate gyrus*; 2 = *columns of the fornix*; 3 = *indusium griseum*; 4 = *medial mamillary nucleus*; 5 = *lateral mamillary nucleus*; 6 = *ventromedial nucleus of the hypothalamus*; 7 = *septal nuclei*; 8 = *nucleus accumbens*.

In these diagrams fibre tracts are delineated with thick lines and cell masses with thin lines. Terminal degeneration is indicated by dots and operative lesions in solid black. An interrogation mark has been placed where a structure has not been examined histologically.



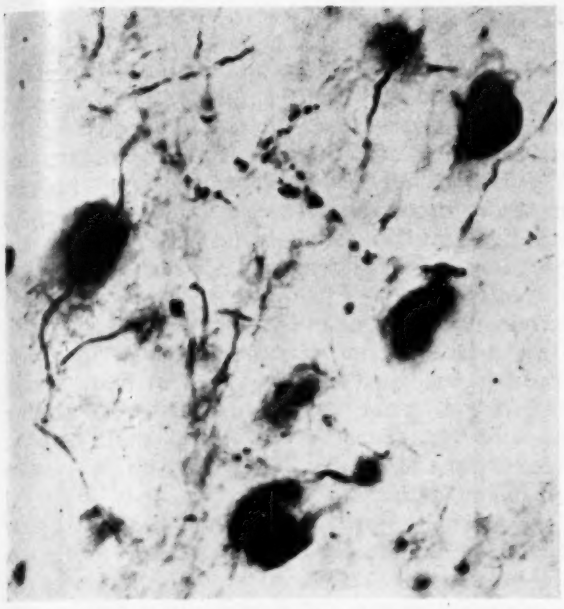


FIG. 2.—Pericellular fibre degeneration in the lateral septal nucleus (Experiment 6) Glees stain × 1600.

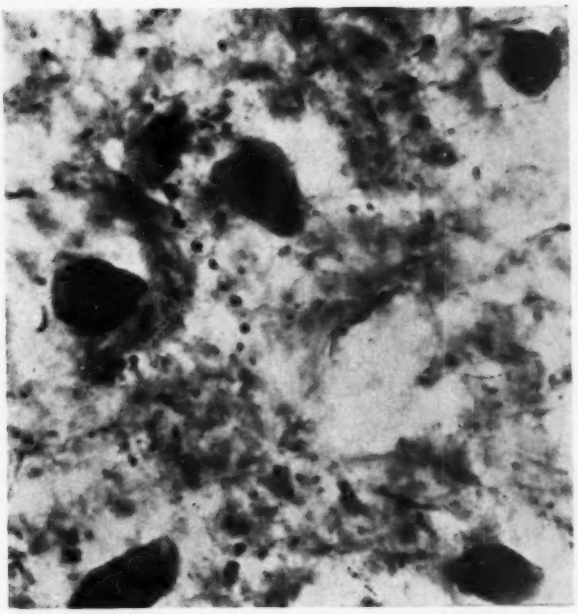


FIG. 3.—Pericellular fibre degeneration in the ventro-medial nucleus of the hypothalamus (Experiment 6). Glees stain × 1350.

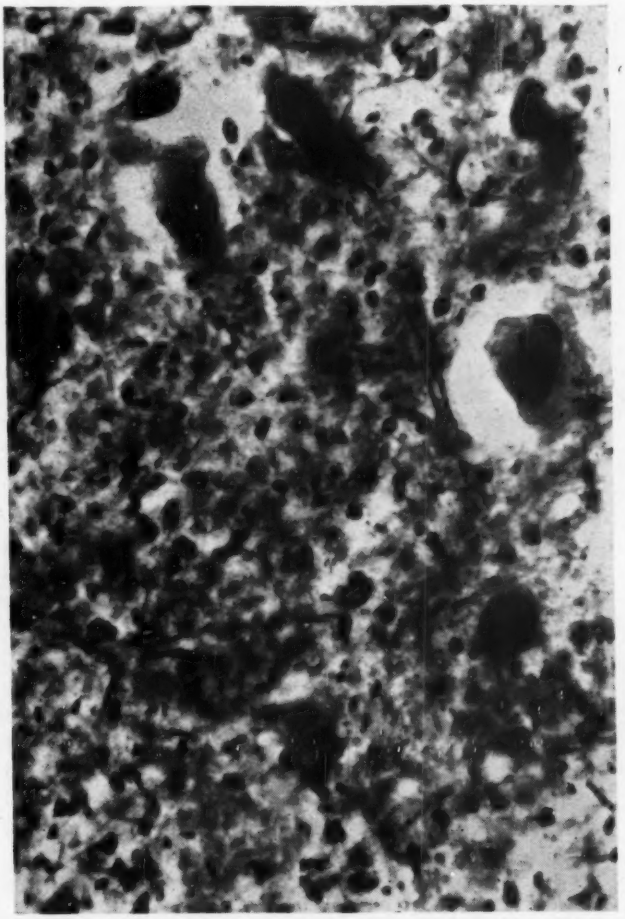


FIG. 4a.—The normal appearance of the medial mamillary nucleus stained by the Glees method. The photograph is taken from a section of the mamillary body in Experiment 6, and shows an unaffected area of the medial nucleus in which there is no degeneration. × 1350.

FIG. 4b.—The same section showing numerous degenerating boutons terminaux in a more dorsal part of the medial mamillary nucleus. × 1350.

FIG. 6.—Injury to the anterior portion of the left hippocampus (Experiment 1).

Experiments

Experiment 1.—The subject, a *Macaca mulatta*, " Minnie," received at operation an injury of the anterior hippocampus (Fig. 6).

This monkey, whose brain was supplied by the courtesy of Dr. G. Weddell, was operated on in an attempt to sever the sensory root of the left trigeminal nerve. Access was obtained through the middle cranial fossa and, in retracting the temporal lobe, the uncus and the adjacent extremity of the hippocampus were damaged. Complications necessitated re-exposure of the trigeminal nerve root, and it is consequently uncertain precisely when the lesion was inflicted ; it must have occurred between five and seven days before death. The animal was killed with nembutal and perfused with formol saline ; the brain was then removed and hardened in formaldehyde. This narcotic and this method of fixation have been employed in all subsequent experiments, with the exceptions of Nos. 3 and 4.

Examination.—The lesion extends obliquely across the ventral surface of the left temporal lobe in a rostral and medial direction. The amygdaloid complex has been injured, and the anterior extremity of the hippocampus is destroyed.

The hippocampi were embedded in gelatine and cut horizontally. Injury is seen to affect both the rostral tip of the left hippocampus and the dentate gyrus. Microscopical examination of the right hippocampus was unsatisfactory, due to a technical error in histological preparation.

The diencephalon was cut coronally and selected sections examined. In the mamillary region, very large numbers of boutons terminaux are present in the ventral part of the left medial mamillary nucleus. Some of them show unequivocal signs of degeneration, though there are no changes in neighbouring fibres. Caudally, about a quarter of the medial mamillary nucleus is so affected, but more rostrally only the most dorsal part is free from boutons (see Fig. 13). A very few boutons, showing in isolated instances suggestions of degeneration, are seen in the right medial mamillary nucleus, but they are probably of no significance. The left lateral mamillary nucleus contains a few swollen boutons terminaux ; as none are seen in the corresponding right nucleus, some importance attaches to them. The left nucleus intercalatus, in this brain a well defined cell mass, shows numerous degenerating boutons terminaux in its ventral part. A few degenerating fibres are also seen in the left supramamillary nucleus.

In the main part of the hypothalamus there is bilaterally massive pericellular fibre degeneration in the region of the ventromedial nucleus. No abnormality is seen in the perifornical nucleus, nor in the other hypothalamic nuclei. The fornix itself is not, at this early stage, abnormal in appearance.

There is unequivocal fibre degeneration in the most ventral part of the lateral septal nucleus, the n. septoventricularis of Brockhaus (1942). The identification of this nucleus, however, is uncertain ; some of the degeneration appears to lie rather in the " fundus subventricularis medialis " of the same author, which corresponds with the most medial part of the nucleus accumbens of other authors. Both sides are affected. The rest of the n. accumbens, the tuberculum olfactorium, the nucleus of the diagonal band, and the other septal nuclei appear to be normal.

The habenulae and the brain-stem were not examined. No degeneration was seen in the indusium griseum or in the cingular gyrus.

Experiment 2.—The subject was a *Macaca mulatta*, MF94, and a transcallosal fornicotomy (Fig. 7) was performed.

The corpus callosum was exposed by a left parietal osteoplastic craniotomy ; after retraction of the left cerebral hemisphere, the peri-callosal branches of the left anterior cerebral artery were coagulated and the corpus callosum incised sagittally. This incision was deepened until the third ventricle was visible ; a right-angled steel hook, designed for the purpose, was then passed through the incision and rotated so as to lie in the coronal plane. It was then withdrawn in this position with the intention of severing the fibres of the fornix. The monkey was permitted to survive for eight days, during which time it exhibited a right spastic hemiplegia with intermittent seizures of a Jacksonian character. The brain was hardened in the manner described in the first experiment.

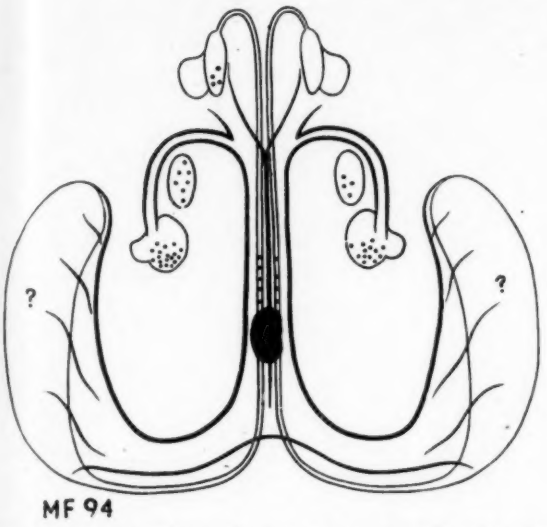


FIG. 7.—Bilateral partial section of the fornix column (Experiment 2).

Examination.—Gross inspection, supplemented by dissection under the binocular microscope, shows that rather more than half of the corpus callosum was injured ; there is fairly extensive softening of the medial surface of the left parietal lobe, involving the cingular gyrus. Both fornices have been injured, but neither completely severed. The diencephalon and anterior fornix were sectioned sagittally. Very numerous boutons terminaux are seen in the dorsal and caudal part of the medial mamillary nuclei (see Fig. 14) ; both sides are so affected, the left more extensively. The areas exhibiting this terminal degeneration are quite sharply demarcated, as is shown in the figure. No fibre degeneration is seen in the mamillary capsule. Of the minor mamillary nuclei, the nuclei intercalati, which are not easily defined in sagittal section, appear severely affected ; the left supramamillary nucleus is normal and the left lateral mamillary nucleus probably so.

In the more rostral part of the hypothalamus there is definite fibre degeneration in a region corresponding with the rostral extremity of the ventromedial nucleus. The changes are more marked on the left side, but are present also on the right. The paraventricular, perifornical, and preoptic regions show no degeneration ; the lateral hypothalamic area was not adequately examined.

The fornices show signs of local injury on their medial sides ; retraction bulbs of Cajal are seen. However, the horizontal and descending portions of the fornix do not at this stage show signs of degeneration. Fibres of the pre-commissural component of the fornix lying ventral to the corpus callosum can be traced to the diagonal bands, but their further course is obscure.

There are a few degenerating fibres in the ventral part of the lateral (parvocellular) septal nucleus on the left side ; the right appears to be unaffected. No degeneration is seen in the nucleus accumbens, the tuberculum olfactorium, or the nucleus of the diagonal band. Study of apparently undegenerated fibres of the fornix suggests, however, that this tract contributes to the diagonal band itself (c.f. Ariëns Kappers, Huber, and Crosby, 1936), though this cannot be determined with certainty. A few boutons terminaux are visible in the right medial habenular nucleus but, being neither numerous nor obviously swollen, are in themselves not conclusive evidence of terminal degeneration.

On both sides the striae Lancisii were severed in the splitting of the corpus callosum. Traced rostrally from the lesion, the medial striae exhibit severe degeneration, especially in the dorsal stratum ; the more ventral fibres are degenerated only in the immediate vicinity of the lesion. There are some boutons terminaux among these fibres, suggesting axo-dendritic synapses, and a few are also present among the neurons of the indusium griseum. The material does not allow the degenerated fibres to be followed as far as the genu ; none of the fibres penetrating the corpus callosum are degenerated. The two hippocampi were embedded, sectioned in a plane transverse to their long axes, and stained with methylene blue ; no retrograde changes could be detected.

Experiment 3.—The subject was a *Macaca mulatta*, MF98, and a transcallosal fornicotomy (Fig. 8) was performed.

The corpus callosum was exposed and incised in the manner described in the previous experiment, and the

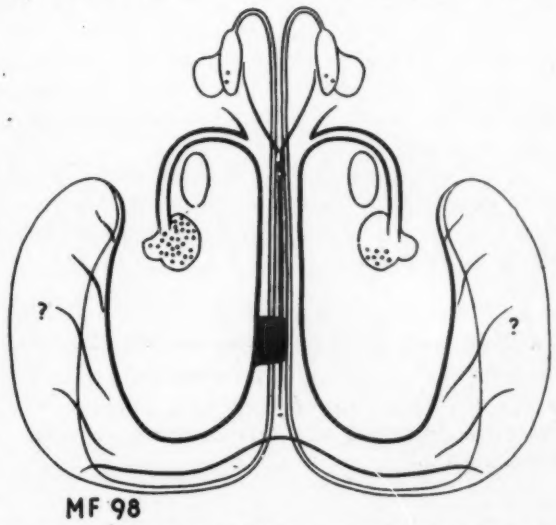


FIG. 8.—Section of the left fornix column and partial section of the right (Experiment 3).

fornicotomy hook passed through the incision and rotated so as to lie athwart the left fornix. Diathermy current was then applied to the hook.

The monkey's condition after the operation was poor : it exhibited a right-sided hemiplegia and died six days after the operation. Necropsy showed hypostatic pneumonia and a severe nematode infestation of the colon ; there was no intra-cranial infection or massive haemorrhage. The brain was hardened in formalin without perfusion.

Examination.—The brain was sliced in the coronal plane. The left fornix is seen to be cut in two places ; it is grey and gelatinous in consistency. There are small haemorrhages and softening in the cingular gyrus, the pulvinar, and the dorsal thalamus ; the internal capsule and basal ganglia are macroscopically intact. The diencephalic injury greatly reduces the value of this brain, and microscopic examination has been therefore limited to the site of injury, the mamillary nuclei, and the septal region.

A block containing the damaged fornices was embedded in paraffin and cut horizontally. Sections show the left fornix to be severely injured and probably wholly divided. There appears also to be injury in the contiguous, medial part of the right fornix ; but at this level the close approximation of the fornix columns makes distinction difficult.

Selected blocks from the diencephalon were sectioned coronally. Boutons terminaux are seen in both medial mamillary nuclei ; they are however less numerous and less strongly argyrophilic than those seen in other experiments, and their distribution is not easy to plot. On the left, the whole medial mamillary nucleus is apparently affected, but most severely in its dorsal portion. On the right, only a small area in the caudal and dorsal part contains boutons. A few boutons terminaux are seen in the left lateral mamillary nucleus but they are too few to constitute certain evidence of a projection to this structure. The nuclei intercalati are poorly developed, and the left nucleus cannot be defined ; there is terminal degeneration in the right nucleus.

In the septal region there is very scanty bilateral fibre degeneration in the lateral septal nuclei, and possibly also in the immediately adjacent portion of the n. accumbens.

Experiment 4.—The subject was a *Macaca mulatta*, MF99, and the operation a transcallosal fornicotomy (Fig. 9).

The left fornix was injured with diathermy ; the operative procedure was similar to that adopted in Experiment 3.

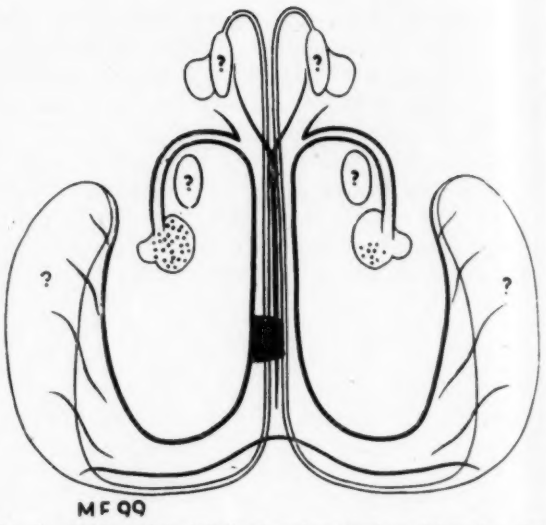


FIG. 9.—Section of the left fornix column and partial section of the right (Experiment 4).

Post-operatively the monkey showed signs of severe neurological affection, including a right-sided hemiplegia, a left oculomotor palsy, and a rhythmic tremor of the head, and on the fifth day it died. The brain was hardened without perfusion. Necropsy showed no extracranial disease of any importance.

Examination.—The brain shows no evidence of infection or compression. However, there are numerous punctate haemorrhages in the left thalamus and basal ganglia, with displacement of the ventricular system to the right. The left fornix is apparently severed. As with Experiment 3, such extensive injury greatly complicates the interpretation of any degeneration, and only the lesion and the mamillary bodies have been examined microscopically.

A block containing the injured fornices was embedded in paraffin and cut horizontally. The left fornix has been totally divided ; there is probably minor damage to the medial side of the right fornix. The lesion is therefore almost the duplicate of that in Experiment 3, and the distribution of terminal degeneration in the medial mamillary nuclei as seen in coronal sections (Fig. 13) is almost identical. Boutons terminaux in significant numbers are seen in both medial mamillary nuclei, in the whole volume of the left, but mainly in the dorsal part caudally of the right. As in Experiment 3 the distribution is not easily defined, probably because the shorter survival times give less obtrusive signs of terminal degeneration. The nuclei intercalati are small and spherical in this brain ; both contain degenerating boutons. No certain evidence of terminal degeneration can be seen in the lateral mamillary nuclei.

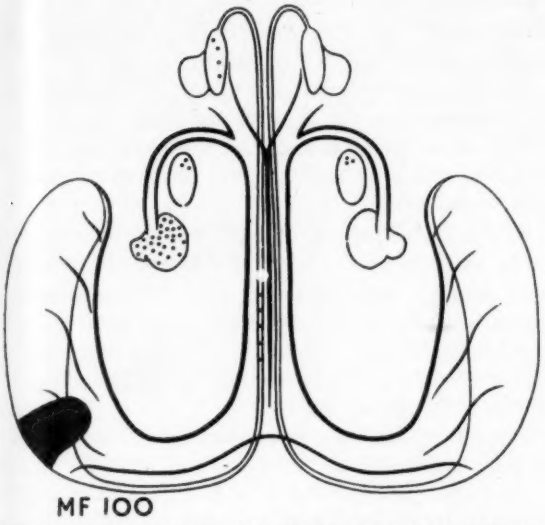


FIG. 10.—Injury to the posterior portion of the left hippocampus (Experiment 5).

Experiment 5.—A *Macaca mulatta*, MF100, at operation received an injury of the posterior hippocampus (see Fig. 10).

The posterior part of the left temporal lobe was exposed by the reflection of a small osteoplastic flap; the middle temporal gyrus was incised with diathermy, and this incision was deepened with a fine-calibre sucker until the hippocampus was visible. A lesion was made by suction as far posteriorly as possible in the substance of the hippocampus. Post-operatively the monkey showed no signs of neurological injury; it showed, however, a definite change in behaviour, becoming less suspicious of its attendant. On the tenth day it was killed.

Examination.—External examination of the brain shows only the operational wound. A block containing the whole left hippocampus was embedded and sectioned in the transverse plane. Representative sections were stained with methylene blue and with iron haematoxylin. The lesion is seen to involve the caudal end of the hippocampus and dentate gyrus and the lateral half of the fimbria at the corresponding level. The most caudal extremity of the hippocampal complex has escaped injury; rostral to the lesion the hippocampus and dentate gyrus appear normal, though the partial section of the fimbria must have severed many of their axons. The lesion does not involve the stria terminalis macroscopically; however, this tract shows some dubious fibre degeneration in sections stained by the Glees method. The major part of the entorhinal area escaped direct injury, but the temporo-ammonic tracts must have been interrupted in the hippocampal lesion.

The mamillary region was examined in sagittal section. The left medial mamillary nucleus contains very numerous boutons terminaux; many of them show obvious signs of degeneration. Their distribution is shown in Fig. 14. They are accompanied by fine degenerating preterminal fibres, not seen in previous experiments. The left nucleus intercalatus contains a few degenerating fibres. The left lateral mamillary nucleus contains numerous degenerating terminals. The right medial mamillary nucleus exhibits a very small number of boutons terminaux; though these are occasionally seen in normal preparations, the possibility of a projection by a few fornix fibres to the contralateral medial mamillary nucleus cannot be definitely excluded. In the hypothalamus there is bilateral pericellular degeneration in a region corresponding to the junction of the ventromedial nucleus with the anterior hypothalamic area; it is probable that both these cell groups are affected. The perifornical region and the fornices themselves show no detectable change. Attempts to trace fornix fibres into the midbrain were unsuccessful, but the existence of such fibres cannot be excluded.

In the septal region (examined in sagittal section) terminal degeneration is seen in the dorsal part of the left lateral septal nucleus. Degenerating fibres are also seen passing horizontally through the septal nuclei; the appearances suggest that these fibres are going to the diagonal band, but this cannot be certainly determined. No degeneration is seen in the nucleus accumbens, the tuberculum olfactorium, the nucleus of the diagonal band, or the right septal nuclei.

Sections of the habenular nuclei show no degeneration but the sections taken in this region are poor in quality.

The striae Lancisii and indusium griseum were examined, also in sagittal section: the left medial stria shows degenerating fibres running dorsal to the neurons of the indusium; a few degenerating boutons de passage are seen between the fibres. The right stria appears normal.

The right hippocampal region was sectioned horizontally. Careful examination of the hippocampus and dentate gyrus reveals no abnormality; portions of subiculum, entorhinal area, and of the amygdaloid complex were also examined and no degeneration seen.

Experiment 6.—The subject was a *Macaca mulatta*, MF101, and the operation transcallosal fornicotomy (Fig. 11).

The splenium of the corpus callosum was exposed by the elevation of a large right occipito-parietal osteo-

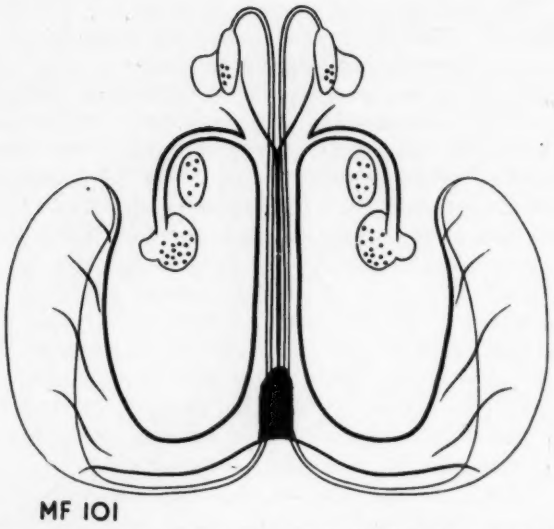


FIG. 11.—Bilateral partial section of the fornix columns and the psalterium (Experiment 6).

plastic flap. The pericallosal branches of the anterior cerebral vessels were coagulated and the splenium completely divided in the median line. It was hoped by this manoeuvre to sever the psalterium. The fornices were seen and lesions made in the right fornix without the use of diathermy. Post-operatively the monkey's condition was excellent and, as in the previous experiment, it was definitely more docile than before the craniotomy. Thirteen days after the operation the monkey was killed.

Examination.—Externally the brain shows no damage or disease, other than the wound in the corpus callosum.

A block including the damaged fornix and the surrounding structures was embedded and sectioned horizontally. There are infarctions in both cingular gyri, due no doubt to the coagulation of the cortical branches of the anterior cerebral arteries. The corpus callosum has been divided for a distance of 1–1½ cm. The adjacent, medial sides of both fornices have been injured, the left more severely. The psalterium has presumably been divided, but this commissure cannot be identified. There is no macroscopic evidence of injury to the striae terminales, but sections of these tracts, cut parallel to their fibres, show possible signs of degeneration in the right stria.

The mamillary nuclei were examined in coronal section. Both medial mamillary nuclei contain degenerating boutons terminaux in their caudal and dorsal portions (see Fig. 13); the area involved is considerably more extensive on the left side. The supramamillary nuclei are not affected. A few boutons are seen in both lateral mamillary nuclei. The left nucleus intercalatus, which is poorly demarcated, contains degenerating boutons; the right nucleus could not be defined at all.

In the hypothalamus, sectioned coronally, there is exceedingly severe pericellular fibre degeneration in both ventromedial nuclei. The remainder of the hypothalamus, including the perifornical nuclei, appears normal.

In the septal region, also cut coronally, there are many degenerating fibres in the ventral parts of both lateral septal nuclei. The area affected is circumscribed, and probably corresponds with Brockhaus' (1942) " n. septo-ventricularis ". The nucleus accumbens and the tuberculum olfactorium appear to be unaffected.

The habenulae were cut coronally. Very massive terminal degeneration, including some bizarre endings, is present in both medial habenular nuclei, but this is almost certainly due to direct injury inflicted when the fornices were divided immediately above the habenulae. The right hippocampal complex was embedded, cut in a plane transverse to its long axis, and stained with thionin. No chromatolysis is seen in the cells of hippocampus, subiculum, or entorhinal area. The left hippocampal complex was cut in the same plane, and selected sections stained with the method of Glees. No degeneration is seen in the alveus, hippocampus, dentate gyrus, subiculum, or entorhinal area.

Experiment 7.—The subject, a *Cercopithecus sabaeus*, MF102, received at operation an injury of the central part of the hippocampus (Fig. 12).

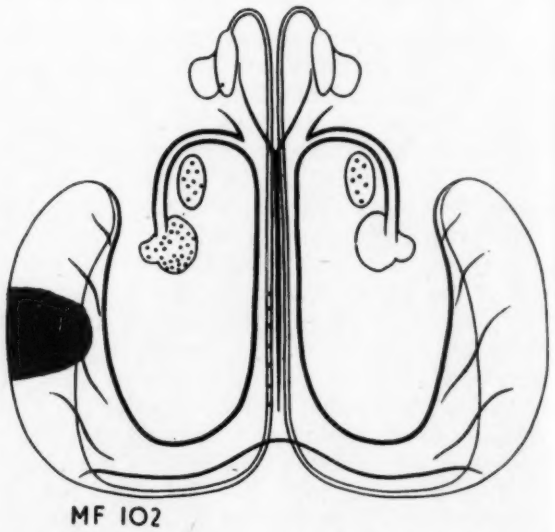


FIG. 12.—Injury to the central portion of the left hippocampus (Experiment 7).

The left temporal lobe was exposed through an enlarged trephine hole, and the middle temporal gyrus incised with diathermy. The incision was deepened, in a medial and ventral direction, until it was estimated that the hippocampus had been traversed. Haemorrhage prevented identification of the hippocampus and lateral ventricle. Post-operatively, there were no obvious neurological defects ; however, the monkey, which had previously exhibited a morose and even spiteful disposition, was decidedly more docile. Seven days after the operation, the monkey was killed.

Examination.—Externally, the brain showed no disease or injury other than the operation wound. A block containing the left hippocampus was embedded and cut sagittally. Sections show the lesion as a cavity about 1 cm. in diameter penetrating the temporal lobe from its lateral surface medially as far as the hippocampus. The central third of the hippocampal complex is totally destroyed ; the fimbria is injured but numerous fibres in it appear to have escaped destruction. The stria terminalis has been severed ; the amygdaloid nuclei are intact.

The brain-stem and posterior diencephalon were cut, as a single block, in the sagittal plane. The left medial mamillary nucleus contains numerous degenerating boutons terminaux, especially caudally; the distribution is shown in Fig. 14. The right medial mamillary nucleus contains no significant evidence of terminal degeneration. The left lateral mamillary nucleus exhibits a small but abnormal number of boutons terminaux. The left nucleus intercalatus is large but ill-defined ; it contains many degenerating terminals.

The pontine and tegmental nuclei, and especially the ventral tegmental nucleus of Tsai (1925) and the reticular formation, have been carefully examined ; their anatomy is difficult to establish in sagittal section. No terminal degeneration is seen, but it is possible that minor changes have escaped notice. An unsuccessful attempt was made to trace undegenerated fibres from the fornix to the tegmentum ; if such fibres do exist, they must be diffuse and not, as in the rabbit, a compact bundle.

In the hypothalamus the ventromedial nuclei are filled with most severe pericellular degeneration ; other nuclei appear normal.

The septal region, horizontal fornices, and corpus callosum were sectioned sagittally. The septal nuclei show unexpectedly little terminal degeneration : careful search reveals only a few fragmented fibres in the ventral part of the left lateral septal nucleus.

In the left medial stria Lancisii there is well-marked degeneration of long fibres and of boutons de passage. There is also some terminal degeneration around the cells of the left indusium griseum. No abnormality is seen on the right side. The habenular nuclei, examined in sagittal section, appear normal.

The right hippocampus was sectioned transversely to its long axis. No degeneration is seen in dentate gyrus, hippocampus, or subiculum ; the entorhinal area was only partially examined, but appears unaffected.

Supplementary Experiments

The following experiments were performed by Adey and Meyer in the course of a study (to be published) of the connexions of the temporal pole. By the courtesy of these authors, they are reported here in so far as they concern the present study.

Experiment 8.—The subject was a *Cercopithecus sabaeus*, M85.

In this brain there is a massive lesion involving almost the whole of the amygdaloid complex and extending into the entorhinal area and the anterior tip of the hippocampus itself.

Boutons terminaux are present in the most ventral part of the ipsilateral medial mamillary body, occupying an area rather more extensive rostrally than caudally. The area affected resembles that described in Experiment 1 very closely, but is smaller in the dorso-ventral dimension.

Experiment 9.—The subject was a *Cercopithecus sabaeus*, M91.

In this case the lesion is restricted to the entorhinal area and amygdaloid complex. The hippocampal formation is mainly intact, save for a small lesion with inflammatory reaction in the alveus anteriorly. The ipsilateral medial mamillary nucleus, examined in coronal section, shows a very small but unquestionably significant number of boutons terminaux in its most rostral and ventral part.

Experiment 10.—The subject was a *Cercopithecus sabaeus*, M86.

In this brain the lesion involves the amygdaloid complex, with the exception of its medial and cortical nuclei and the nucleus of the lateral olfactory tract ; in consequence, the stria terminalis has degenerated. A portion of the superior temporal gyrus and the prepiriform cortex have been destroyed, but the hippocampus is uninjured. No terminal degeneration is seen in those parts of the medial mamillary nuclei which were affected in the two preceding experiments.

Discussion

The present study was planned to give a comprehensive picture of the efferent projection of the hippocampus in the monkey, with special reference to speculations upon its possible functions. The aim has been only partially successful. There remain important lacunae in the data which express the limitations of the ammoniacal silver method, at least in the writer's hands, and the technical difficulty of interrupting the fornices without coincidental damage to adjacent structures. However, certain conclusions may be stated with some confidence. The hippocampus projects to the medial mamillary nucleus of the same side. The fibres terminate in all parts of the medial mamillary nucleus and there appears to be fairly precise spatial correlation between their origins and terminations. This is well seen in the coronal and sagittal sections of mamillary

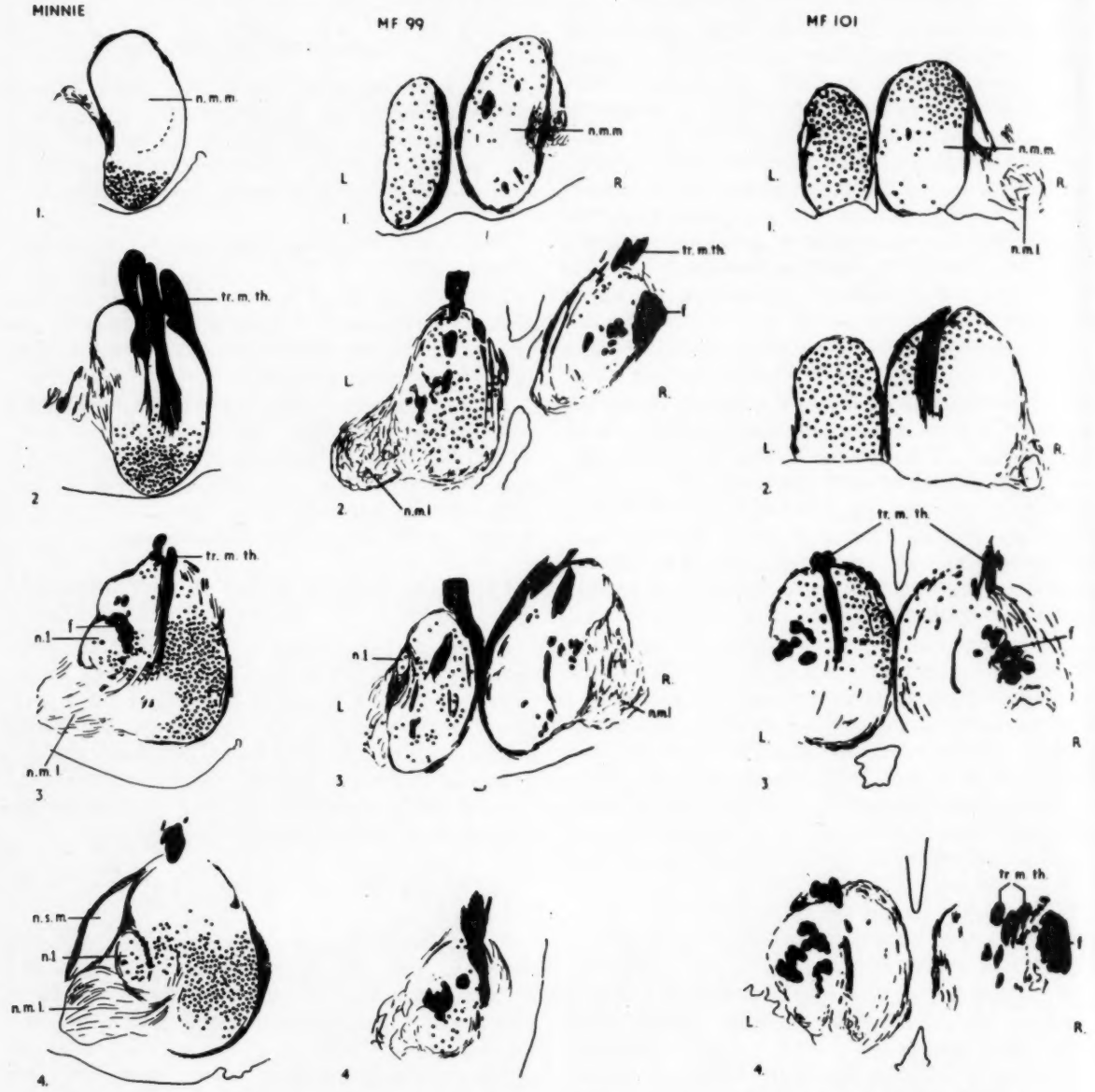


FIG. 13.—The mamillary bodies in Experiment 1 (Minnie, left side only), Experiment 3 (MF99), and Experiment 6 (MF101) × 12.
The drawings are made with the camera lucida from coronal sections ; the presence of terminal degeneration is indicated by dots whose density corresponds approximately with that of the terminal degeneration.
tr.m.th. = mamillo-thalamic tract ; f = fornix ; n.m.m. = medial mamillary nucleus ; n.i. = nucleus intercalatus ; n.m.l. = lateral mamillary nucleus.

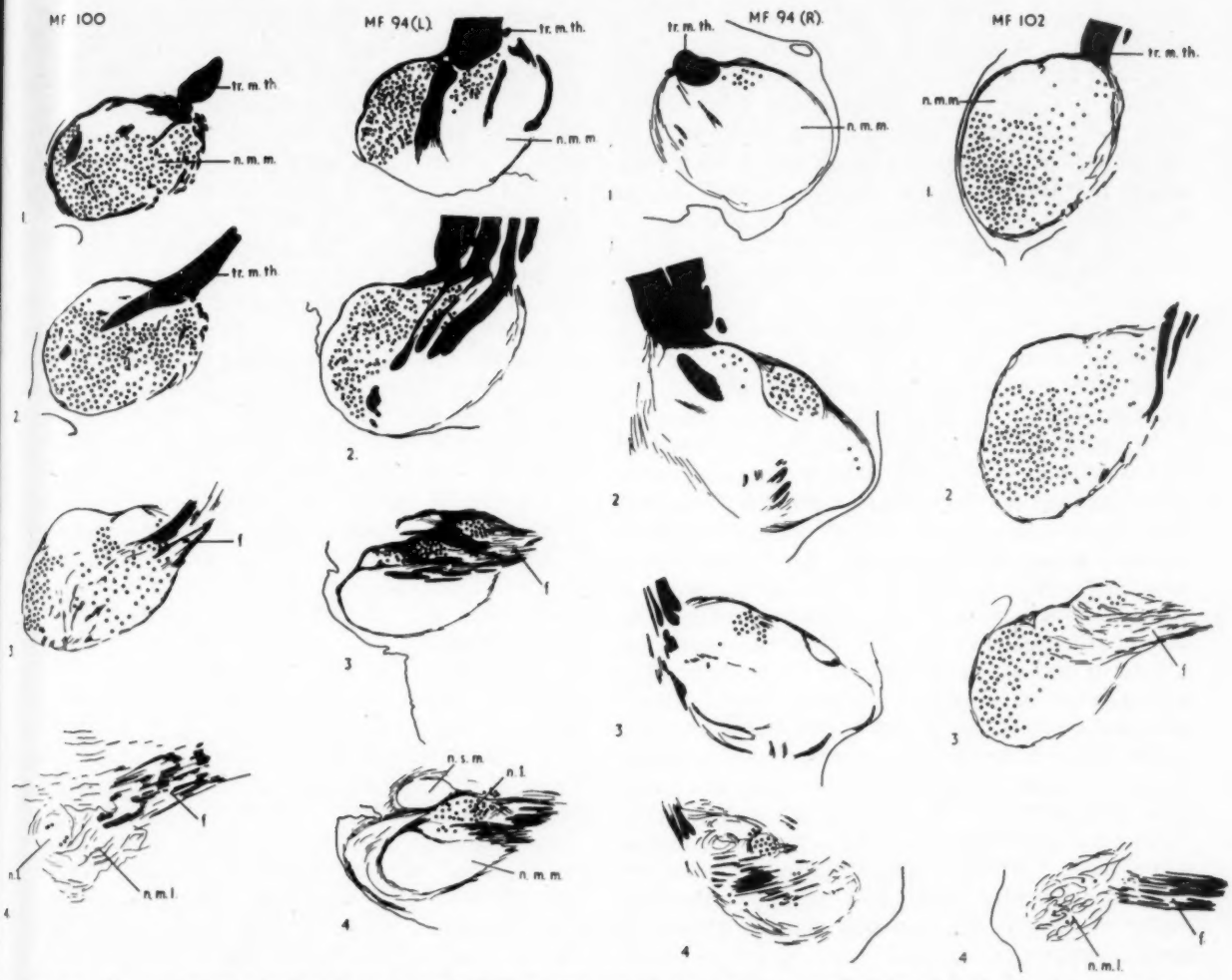


FIG. 14.—The mamillary bodies in Experiment 2 (MF94, both right and left sides), Experiment 5 (MF100, left side only), and Experiment 7 (MF102, left side only) × 12.
The drawings are made with the camera lucida from sagittal sections.

bodies illustrated in Figs. 13 and 14, contrasted with the diagrams which show the various lesions. For the purposes of description, the medial mamillary nucleus may be regarded as an oval mass, at the rostral and dorsal pole of which the mamillothalamic tract emerges; the long axis is thus disposed obliquely to the horizontal plane. The distribution of terminals indicates a stratification in layers parallel to this long axis. Thus the anterior extremity of the hippocampus projects to the ventral and rostral level (Experiment 1 and the Supplementary Experiment 8), and the central part of the hippocampus projects to the axial zone (Experiments 5 and 7). The most caudal and dorsal stratum, which is unaffected in Experiments 1, 5, 7, and 8 presumably receives fibres from the most caudal portion of the hippocampus. An alternative explanation of the absence of degeneration in these experiments is that this unaffected level receives fibres of supracallosal origin, the fornix longus. However, study of two brains with lesions in the cingulate gyrus gives no evidence to support this hypothesis. Experiments 2, 3, 4, and 6 suggest that there is an orderly marshalling of fibres in the fornix also, the most medial fibres projecting to the dorso-caudal stratum of the medial mamillary nucleus. Gross dissections demonstrate that the posterior fibres of the alveus run medially in the fornix, and the anterior fibres laterally. The nucleus intercalatus also receives a fornix contribution. The lateral mamillary nucleus appears to receive a few fornix fibres, but except in Experiment 6 the number of terminals was not large. All previous investigators have described fornix fibres proceeding to

the mamillary body, but the strikingly orderly arrangement of terminals seen in the monkey has not been reported in lower mammals. Moreover, Ramon y Cajal (1909), whose Golgi preparations were made on rodent and cat brains, states that the component of the fornix which ends in the mamillary region is smaller than that passing caudally to the tegmentum; this is certainly not the case in the monkey. Several earlier workers have described a more considerable projection to the lateral mamillary nucleus than is demonstrable in the monkey (e.g. Gerebtzoff, 1941–42); however, this may be a consequence of the use of the Marchi method which does not permit certain identification of the ultimate destiny of fine fibres.

No evidence for a supramamillary decussation was obtained; this decussation is described in the rabbit by Vogt (1898) and by Edinger and Wallenberg (1902). The last named authors observe that there appears to be a difference in the proportion of decussating fibres between different varieties of rabbit, which is of significance in view of the inability of Gerebtzoff (1941–42) and Sprague and Meyer (1950) to find any decussation in their preparations of rabbit brains. A tegmental overshoot of the fornix was not demonstrated. While the possibility that a few fornix fibres pass into the tegmentum cannot be excluded, it seems certain that there is no considerable bundle such as is seen in the rabbit (Edinger and Wallenberg, 1902; Yamagata, 1929; Gerebtzoff, 1941–42). Functionally, of course, the mamillo-tegmental tract provides an alternative route whereby fornix impulses may be relayed to the tegmentum.

Experiments 6 and 8 demonstrate unequivocally that the hippocampus is intimately connected with the striae Lancisii and indusium griseum, as might be expected from the comparative anatomy of these structures.

The precommissural connexions of the fornix have been much more difficult to determine. Study of normal material shows that a large component of fornix fibres extends rostral to the anterior commissure, and the fibre counts reported in this paper suggest that this component is considerably larger than the contribution to the mamillary nuclei. Yet in our experiments terminal degeneration has been seen only in the lateral septal nucleus and is here by no means extensive. It is of course probable that some of the fibres in the precommissural fornix are septal efferents, as described by Gerebtzoff (1941–42), Morin (1950), Sprague and Meyer (1950), and Stoll, Ajmone-Marsan, and Jasper (1951); Allen (1944), however, denies their existence. Also to be considered is the possible presence of a forward extension of commissural fibres such as Tumbelaka (1915) identified both in the brain of an acallosal monkey and in normal material. It yet remains likely that the precommissural fornix includes hippocampal efferents not made evident in this study. These fibres may perhaps be distributed beyond the septum to more remote areas by way of the diagonal band and medial forebrain bundle.

The position regarding a hippocampal projection to the main part of the hypothalamus is also unsatisfactory. Terminal degeneration was seen in the ventromedial nucleus of the hypothalamus in all experiments in which this region was examined, but it is known (Adey and Meyer, personal communication) that this nucleus receives a projection from the amygdaloid complex, and damage either to the latter or to its efferent tract, the stria terminalis, can be excluded in none of these experiments. However, from a careful consideration of the experimental evidence, it seems probable that the fornix does send a small contribution to the region of the ventromedial nucleus, though positive confirmation of this is needed. The absence of changes in the perifornical nuclei is unexpected and of some interest; Sprague and Meyer (1950) observed terminal degeneration in this region in the rabbit.

Negative evidence is presented with some reluctance, as it is only too easy to miss minor degrees of terminal degeneration. But the absence of terminal degeneration in the habenular nuclei is probably of significance. Several authorities, notably Gerebtzoff (1941–42), have described fornix fibres ending in the habenular nuclei and even in the pineal body, but as Vogt (1898) and Sprague and Meyer (1950) have pointed out, it is difficult to section the fornix without concurrent injury to structures known to project toward the habenular region, such as the stria medullaris and the fasciculus septo-thalamicus. Experiments 5, 6, and 7 strongly suggest that the hippocampal commissure is an unimportant structure in the monkey, and this is in accord with the studies of normal material made by Beevor (1891). It had been hoped that a study of retrograde degeneration would decide whether cells other than the hippocampal pyramids and the cells of the indusium griseum contribute axons to the fornix, an important question which has attracted surprisingly little attention. However, in Experiments 2 and 6 no chromatolytic changes were evident, probably because of the short survival times. Experiments 9 and 10 suggest that the amygdaloid complex sends no fibres to the mamillary nuclei. The entorhinal area may possibly do so, but this is considered unlikely; the small number of degenerating terminals seen in Experiment 9 can be accounted for by

the accompanying lesion in the alveus. It may be concluded, therefore, that the commonly accepted view is correct, that the fibres of the fornix destined to the mamillary body are of strictly hippocampal origin. Whether this is true of those fibres which terminate in the septum, however, is an open question. In the recent electroneuronographic study by Stoll, Ajmone-Marsan, and Jasper (1951), both afferent and efferent fibres were found connecting septal nuclei with " the tip of the temporal lobe ", and travelling in the fornix. Cytoarchitectural data are not included in this paper, but presumably these fibres are of neocortical, i.e., extra-hippocampal, origin.

The experiments reported here, and the study of previous examinations of the efferent projection of the hippocampus, do not permit of formulating functional hypotheses. The functions of the mamillary nuclei are still obscure. Their most important projection is to the anterior thalamic nuclei, which in turn project to the cingulate cortex, and it may well be of significance that the primate hippocampus is related so intimately, and with such a sharp spatial localization, to the medial mamillary nucleus. Lower mammals do not show such an arrangement (Sprague and Meyer, 1950).

Papez (1937) presented the interesting hypothesis " that the hypothalamus, the anterior thalamic nuclei, the gyrus cinguli, the hippocampus and their interconnexions constitute a harmonious mechanism which may elaborate the functions of central emotion, as well as participate in emotional expression ". Animal experiments have demonstrated profound behavioural changes after bilateral lesions in the temporal lobes and even after bilateral fornicotomy (Spiegel, Miller, and Oppenheimer, 1940). Various speculative interpretations of these data have been made, and perhaps the most extreme is MacLean's (1949) hypothesis that the structures commonly termed the rhinencephalon constitute a " visceral brain ", associating all forms of sensation with autonomic and emotional activity. However, the hypothesis of direct and specific participation by the hippocampus and fornix system in emotional activities involves a large element of speculation. The results of animal experimentation are by no means in accord and, as the records of the experiments reported in this paper demonstrate, it is extremely difficult to injure the hippocampal system without concurrent injury to the amygdaloid complex and stria terminalis. The absence of gross mental changes after section of the human fornices (Dott, 1938 ; Cairns, 1951) and the apparently normal mentality of a man whose brain shows virtual absence of the fornices due to malformation (Nathan and Smith, 1950), suggest that the hippocampal system subserves some more subtle function. It may be that this function is in the nature of a non-specific activation or regulation of cortical mechanisms, and also of sub-cortical centres, particularly in animals lower in the phylogenetic scale. In this view, the behavioural changes which have been reported in experimental animals following lesions involving the hippocampal system may express a disorganization of normal responses, rather than the interruption of a specific " emotional pathway ". One may postulate that in the human brain other mechanisms can compensate for the defect of hippocampal activity.

Morphology of Terminal Degeneration.—In conclusion, some comments on the morphology of degeneration in this system may be of value. The fibres in the fornix of the monkey are extremely slow to degenerate ; even 10 days after section, the ammoniacal silver method shows no great alteration in the appearance of its fibres. Degenerating boutons terminaux appear however by the fifth day and are still well seen on the thirteenth. It is noteworthy that the fornix appears to terminate solely by boutons in the medial mamillary nucleus, while the degeneration seen in the ventromedial nucleus of the hypothalamus and in the septal region is of the pericellular type. It seems very probable that there is a physiological distinction between these types of ending ; the first is perhaps adapted for transmission to a small local group of cells, the second for a more diffuse type of stimulation. It is interesting to note that Sprague and Meyer (1950) found relatively fewer boutons in the medial mamillary nucleus of the rabbit.

Summary

In the monkey the hippocampus projects to the ipsilateral medial mamillary nucleus, and to a less extent to the lateral mamillary nucleus and the nucleus intercalatus. It is probable that all the fornix fibres destined to the mamillary body originate from the hippocampus, and there is a definite spatial correlation between the cells of origin in the hippocampus and the terminal boutons in the medial mamillary nucleus. It is suggested that this is the most important projection of the primate hippocampus.

The precommissural component of the fornix in the monkey is large, but the destination of these fibres has not been determined with the exception of a small number ending in the lateral septal nucleus. It is probable that many of these fibres are not of hippocampal origin.

The hippocampal commissure is greatly reduced in the primate brain.

It is probable that the primate fornix sends fibres to the ventromedial nucleus of the hypothalamus, but no evidence to support a projection to the habenulae or the tegmentum has been obtained.

The hippocampus projects to the indusium griseum and supracallosal striae.

The fornix fibres end as boutons terminaux in the medial mamillary body, but as pericellular fibre plexuses in the septal region.

I wish to thank Professor W. E. Le Gros Clark, who planned this investigation and has assisted at all stages of its preparation, Mrs. S. Nevin for advice in the interpretation of the sections, and Dr. A. C. Allison for advice on the technique of counting fibres. I wish also to thank Miss Christine Court for the drawings, Mr. L. D. Parke, who prepared much of the histological material, and Mr. F. M. Blackwell for the photomicrographs.

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STUDIES IN TRAUMATIC EPILEPSY

I. FACTORS INFLUENCING THE INCIDENCE OF EPILEPSY AFTER BRAIN WOUNDS

BY

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There is no doubt that epilepsy presents a valuable means of studying cerebral function. Apart from the problem of what factors cause the abnormal neuronal discharge which constitutes the fit, the pattern of attack can give information about the function of the area concerned when the site of injury is known. For this purpose the study of cases of post-traumatic epilepsy following the small penetrating brain wounds of modern warfare is of special value. In this type of injury high velocity metal fragments often cut into the brain without disturbing consciousness, or " explode " a group of bone fragments for a distance of a few centimetres into the brain, while the metal fragment glances away. In either case a highly localized lesion often results, and thanks to the advances of surgery and of the use of antibiotic drugs, most of these wounds were quickly rendered sterile and healed by first intention after *débridement*. The evidence for localization in these small wounds is often precise, and this can be correlated with the content and sequence of events in an epileptic fit. When the wound produces a recognizable neurological deficit, the behaviour of this during the attack can also provide information. For all these reasons traumatic epilepsy has been a constant source of interest, and after the first world war gave rise to many special studies both as regards the incidence of post-traumatic epilepsy and the clinical features of the fits.

The study presented here is concerned with a follow-up of 820 surviving cases of penetrating brain wound suffered during the second world war by British service personnel. During the second war a special effort was made to collect accurate information of cases of brain wounds. The records of this group of cases are carefully preserved and a follow-up system has been kept in operation ever since, by means of a Head Injury Advice Bureau. The records must to some extent depend on postal enquiry, which includes a detailed questionnaire about the fits completed by witnesses, but doubtful cases are re-admitted for further study, and Ministry of Penisons documents are available for consultation. The evidence available as to the nature of faints or fits has been sifted by the writers themselves, and a decision as to the nature of " attacks " has been made on their clinical features, as this is still by far the most reliable method of diagnosis. Electroencephalographic evidence was excluded from the assessment.

Incidence of Post-traumatic Epilepsy

So far as incidence is concerned, recorded figures differ widely. This is due in part to the type of attack accepted as " epileptic ", but partly to variations in the type of injury studied, and also to the differing duration of follow-up after injury. In wounds with definite dural penetration and actual brain damage Wagstaffe (1928) found 27% epileptics, while Gliddon (1943) in a detailed follow-up of 500 cases gave a figure of 66·7% for cases with brain penetration and retained bone fragments. Both these figures are from the 1914 war cases and differences in the length of follow-up account in part for the wide disparity. Other late reviews support a high figure. Thus Ascroft (1941) found a 45% incidence of epilepsy from the records of Ministry of Pensions cases of head wounds with dural penetration. Baumm (1930) gave 44% in a series of 562 cases, while Credner (1930) in one of the largest reported series, quotes the incidence as 49·5% of 1,234 cases. The bare presentation of figures is however to some extent misleading. For example, the patient who has one convulsion in five years and the patient who has a fit every three weeks, though both are suffering from traumatic epilepsy, show very different degrees of cerebral dysrhythmia and disability.

It should be clearly understood that in the present analysis the occurrence of a single epileptic fit or focal attack involves the case being classified as epileptic. On the other hand a few cases which have attacks, the nature of which is uncertain owing

to lack of detail, are classified in this study as *not* having epileptic fits.

Fits which appeared in the early days after wounding are also included, but as one of us has previously (Whitty, 1947) reported, most of these have late epilepsy also. The small number which have fits only in the acute stage are noted separately in some of the tables.

Table I shows that the incidence of epilepsy in this series of 820 cases is already 43% five years after wounding. The length of follow-up in all

TABLE I
INCIDENCE OF EPILEPSY FIVE YEARS AFTER PENETRATING BRAIN WOUNDS

Cases with fits		356 (43%)
Cases with no fits :		
Duration of follow-up :		
over 5 years	403	464 (57%)
2–5 years	21	
1–2 years	21	
at < 1 year	19	
Total		820 cases

non-epileptics is also given, and some of the 61 cases not yet followed-up for five years must certainly have developed epilepsy before that period and so have increased the true incidence of this complication.

So far as disability is concerned, the frequency of fits and their type during the five-year period is shown in Table II for 279 cases where this information was available. It is clear that in over half the cases fits have been very infrequent and are unlikely to be a serious disability.

TABLE II
FIVE-YEAR FOLLOW-UP OF FREQUENCY OF EPILEPTIC FITS

No. of Fits in 5 years	Focal	Generalized	Both	Totals
Less than 5 in all	15	75	40	130
1 or 2 a year ..	12	23	20	55
Over 2 a year* ..	21	44	29	94
Totals ..	48	142	89	279

* In the over-two-a-year group, 20 had had no fits for the last three years of the follow-up period.

Comparison with First World War Cases

It was naturally hoped that the great improvements in surgical treatment in the second world war would reduce the incidence of post-traumatic epilepsy. This hope was based on the generally accepted view (Penfield, 1927) that progressive gliosis is an important factor in the development of an epileptogenic focus, and that as wound infection was abolished and efficient primary *débridement* instituted, so there would be less scarring and the incidence of epilepsy would consequently fall. There is no doubt that the contrast as regards wound infection and thorough *débridement* in the two wars is most striking. In Ascroft's (1941) series only a quarter of the wounds were healed within 15 days, whereas in the second war less than 15% failed to heal by first intention (Cairns, 1948). In spite of this remarkable change, however, the incidence of traumatic epilepsy does not seem to be significantly reduced.

Not only does the figure presented in this series certainly err on the low side, but a considerable number of patients may be expected to develop their first fit at a longer interval after injury than the five-year period used. Baumm (1930), for example, found that 15% of his cases had the first fit more than five years after injury, while in Ascroft's (1941) series this figure was 10%. It is clear, therefore, that the present series in a 10-year follow-up is likely to give figures for post-traumatic epilepsy which will be about 50%, and just as high as those reported from the first war.

Time of Onset of Post-traumatic Epilepsy

The interval after wounding at which the first fit occurred is known accurately in 277 cases. These intervals are indicated in Table III, and they are compared with the figures published by Ascroft and Baumm. There is no obvious explanation for the wide variations in the interval between the injury and the first fit. The effects of progressive scarring here also fail to provide a convincing explanation. The difference may depend partly on the site of wound, and the time of onset in wounds of various areas is shown in Table IV. These figures indicate that for frontal wounds the first fit tends to occur later than for wounds in other regions of the brain. It will also, however, be shown later that frontal wounds tend to cause general convulsions without a remembered aura.

TABLE III
TIME OF ONSET OF EPILEPSY AFTER WOUNDING *

Time of Onset	This Series		Ascroft		Baumm
Under 1 month ..	36		19		
1– 6 months ..	84	181 (73%)	22	56 (75%)	122 (60%)
6–12 ,, ..	61		15		
1–2 years	46	(18%)	10	(13%)	42 (20%)
2–5 ,, ...	21	(9%)	9	(12%)	39 (20%)
Total ..	248		75		203
Over 5 years ..	9		9		37

* Cases with fits only within a month of wounding are excluded (there were 20). Figures for the over-five-year interval are excluded from the percentage analysis as our records are incomplete for this interval.

TABLE IV

COMPARISON OF INTERVALS AFTER INJURY AND FIRST FIT WITH APPROXIMATE SITE OF INJURY

Onset	Frontal	Central	Temporal	Occipital	Totals
Under 1 month only ..	5	11	0	4	20*
Under 1 month	8 11% } 35%	17 14% } 53%	5 26% } 57%	6 18% } 54%	36
1- 6 months	18 24% }	48 39% }	6 31% }	12 36% }	84
6-12 ,, ...	18 24% }	35 29% }	3 16% }	5 15% }	61
1-2 years	20 27% } 65%	16 13% } 47%	4 21% } 42%	6 18% } 45%	46
2-5 ,, ...	10 14% }	6 5% }	1 5% }	4 12% }	21
	74	122	19	33	248
Over 5 years	4	3	2	0	9*
Not known	27	29	5	11	72*

* Excluded from the percentage analysis.

These therefore tend not to have recognizable focal characters, and as Baumm (1930) observed, fits with focal features are more likely to develop soon after wounding. These figures are plotted as curves in Fig. 1, and show that there is a difference in behaviour between frontal wounds and wounds of other regions.

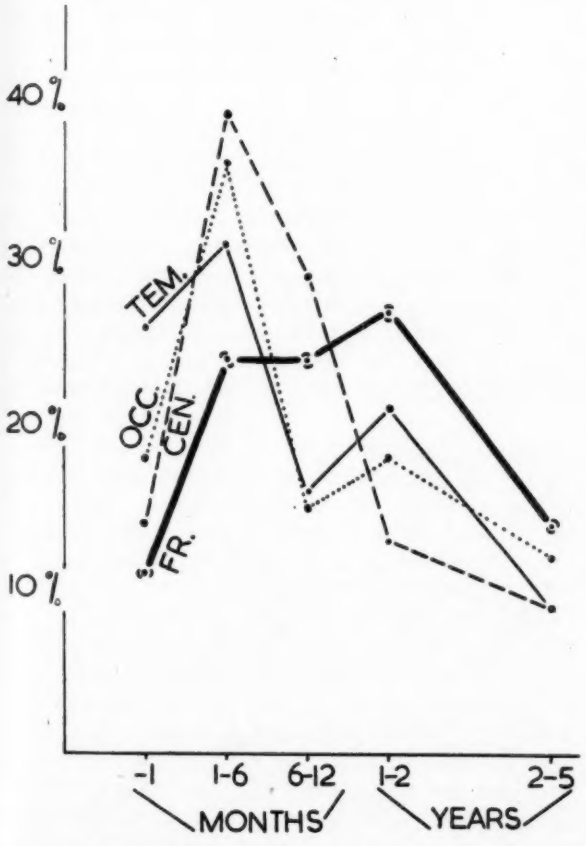


FIG. 1.—The percentage figures from Table IV are charted and illustrate the tendency for epilepsy after frontal wounds (FR.) to develop later than after Central (CEN.), temporal (TEM), or occipital (OCC.) wounds.

Possible Causes of Traumatic Epilepsy

In any given case there are probably several factors contributing to the production of epilepsy. These may be conveniently considered under anatomical and physiological headings. The segregation is artificial but useful. In the first group are site and extent of injury and the secondary effect of sepsis on these ; in the second are the abnormal functioning of groups of neurons in or immediately around a damaged area, irritative lesions, or the functional changes in neurons at a distance from the lesion as a result of the removal of the influence of the destroyed area, release phenomena, or the effects of sepsis on these two mechanisms, and perhaps constitutional predisposition, though this may conceivably also depend on anatomical factors.

Of these factors, sepsis and incomplete *débridement* of dead brain tissue as causes of subsequent progressive scarring have often been considered important. However, as Penfield (1927) points out, where injured cerebral tissue is cleanly removed, such cicatricial contraction is largely eliminated. Our figures, from this series of cases where the incidence of sepsis and incomplete *débridement* have certainly been much lower than formerly, do not support such a view. That acute sepsis of brain or meninges may sometimes precipitate a fit or series of fits must be accepted. One of us (Whitty, 1947) has reported cases in which the occurrence of fits in the acute stage provided the earliest sign of the development of wound infection. In the same way recurrent sepsis in these cases may give rise to recurrent fits. However, the role of early sepsis in the development of later epilepsy seems to be much more uncertain. Superficial wound sepsis has very different and less widespread pathological sequels than those of deep brain infection with prolonged hernia or fungus formation. But even the latter seems relatively unimportant in causing late fits ; for in this series only 54% of 112 cases with early fungus, abscess or meningitis

developed persistent epilepsy, a figure little greater than that provided by the whole series.

Previous writers have pointed out that the site of the brain wound affects the incidence of fits. Ascroft (1941) considered that fits frequently followed wounds around the Rolandic area and diminished in incidence as the poles of the brain are approached, though he utters a caveat about the accuracy of localization in his material. Baumm's figures also support this : 67·7% of fits in the " central parietal region " compared with 15·8% in the frontal and 6·9% in the occipital areas, though Credner (1930) finds a smaller difference with 47·3% parietal and 45% frontal. In Fig. 2 and Table V, the findings in our material are shown. The figures certainly support a higher incidence in the central region.

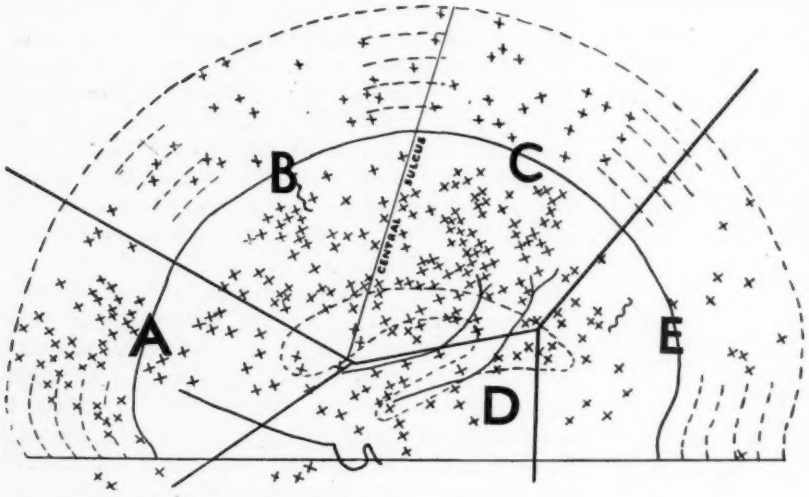
In Fig. 2 the site of wounding is charted for over 600 cases which have either developed epilepsy (X) or have not developed epilepsy at a five-year follow-up (O). Cases which have not reported fits and have been followed up for less than five years are therefore excluded, whereas those reporting fits during a short follow-up period are included. This weights the selection of cases for charting slightly in favour of those developing epilepsy, and for this reason the charted cases show an incidence of epilepsy of 48% as compared to 43% in the analysis in Table I. Table V is prepared from Fig. 2 by comparing the number of Os and Xs in five regions, the dividing lines being as shown in Fig. 2. Thus the percentages shown in Table V also show the bias (about 5%) towards

TABLE V

COMPARISON OF SITE OF WOUND WITH INCIDENCE OF FITS CALCULATED FROM FIG. 2 *

Reference to Fig. 2	Site of Wound	Totals	Cases with Fits
A	Prefrontal and inferior frontal	160	63 (39%)
B	Motor and premotor	127	70 (55%)
C	Parietal lobe	170	111 (65%)
D	Temporal lobe	71	27 (38%)
E	Occipital lobe	73	28 (38%)
	Total	601	299 (48%)

* The Os and Xs are collected from the five regions marked on Fig. 2 as A, B, C, D, E. The higher figure for traumatic epilepsy compared to Table I is explained in the text.



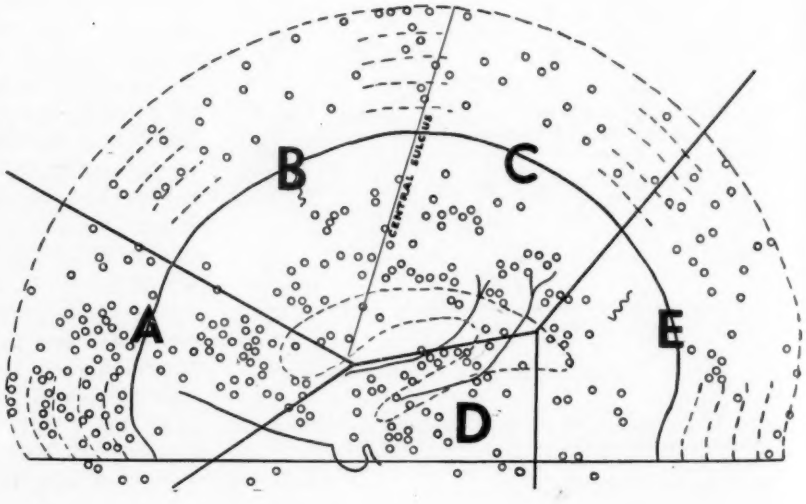


FIG. 2 (a and b).—Charts to show the site of wounding in over 600 cases of penetrating brain wound. Charting depends on measurements taken from skull radiographs (Russell, 1947). Wounds which lie within 5 cm. of the sagittal line are placed in the halo outside of the skull outline. The cases marked X developed post-traumatic epilepsy while those marked O showed no epilepsy at a five-year follow-up. The lines divide the cases into five groups which are compared in Table V (A, B, C, D, and E).

raising the proportion developing epilepsy. The relative incidence of epilepsy in the five regions is, however, clearly shown.

So far as exact extent of wound is concerned, reliable estimates are difficult to obtain, but taking 103 cases with persistent hemiplegia as representing more extensive injuries, the percentage of those with fits is 66. When persistent monoplegia is considered (47 cases), the figure is 47%. It seems therefore that patients with more extensive wounds are only slightly more prone to develop fits, though it must be remembered that a persistent hemiplegia represents not only a more extensive wound, but also a specific anatomical site of wounding, and that this latter factor may be the causal one. If we compare persistent left and right hemiplegias, the percentage of epileptics is little different, being 62% in the right and 72% in the cases of left-sided hemiplegia.

The influence of a constitutional factor has not been considered here, because facilities for obtaining information about epilepsy in the family tree, even when limited to siblings and parents, were not thought to be reliable. Logically this factor may be expected to play some part in incidence, or at least in the frequency with which fits occur.

Mechanisms of Fit Production

All the foregoing factors must finally exert their influence on cerebral physiology in such a way as to produce a fit. The remarkable way in which epileptic phenomena may be reproduced by electric stimulation of the brain (Penfield and Rasmussen, 1950) draws attention to the possibility of traumatic epilepsy being due to a positive irritative phenomenon. It should be pointed out, however, that the spontaneously occurring fit is just as likely to be a release phenomenon.

The occurrence of inhibitory fits, either focal or general, requires to be fitted in with any theoretical conception. These will be studied in their varying forms in a later section. One of us (Russell, 1951) in a preliminary reference to some of these figures has drawn attention to the tendency for a one-to-one ratio to develop between the total numbers of cases of brain wound which do and do not develop fits. Further, Penfield (1952) refers to the cure-rate of traumatic epilepsy by operative excision of a brain scar or focus as about the same (50%). The same figure has been reported by Jooma, Pennybacker, and Tutton (1951) for the incidence of epilepsy after brain abscess. This one-to-one ratio suggests a balance of two equally important factors which may swing towards or against epilepsy developing, according to which of the two factors is most damaged.

There is physiological evidence that neurons have spontaneous discharges which are normally modified, enhanced or decreased by impulses reaching them via the boutons of other neurons (Brazier, 1951). In a group of neurons relatively isolated by trauma to surrounding cells or fibres spontaneous discharges may occur which are largely freed from the normal influence of other cells. If the influence removed is mainly excitatory, reduced discharge will result. This might show itself either as a permanent loss of function of these neurons, or, if the excitation removed was smaller, as an episodic loss of function when for any reason the remaining excitatory impulses reaching the neurons fall below a critical level. *Per contra*, if the removal is mainly inhibitory, an abnormally great discharge will ensue. The nature of the clinical correlate of this discharge, the epileptic fit, will presumably depend on the function of the cells firing. If in the area of the motor cortex, a focal motor attack would result. If the remaining cells were themselves normally of mainly inhibitory function, then the clinical result would be a focal inhibitory attack. The basic physiological lesion in any case would be an upset in the normal balance of influences playing on the various neurons. Such a formulation as the above would account for a focal attack or the "local sign" of a more generalized one. The pathways available to the initial abnormal discharge (availability would be determined both by anatomical considerations, such as the site of the original discharge, the presence of damaged and undamaged fibres, etc., and by physiological considerations such as whether synapses are refractory or excitable) would determine whether and how far the discharge spread, that is, whether the fit became generalized. On such an explanation it would be expected that there would be areas from which generalized fits would be readily excited, and others where focal attacks would be more common; but also that generalized attacks could sometimes be evoked from any area. The fixed anatomical connexions of a region would determine its general tendency for predominantly focal or general response, but the physiological "set" of excitation and inhibition in surrounding neurons at a given moment would determine whether a discharge remained localized or not. This is in fact very much the picture seen in traumatic epilepsy.

So far as the general distribution of wounds is concerned, in this series one of us (Russell, 1947) has previously suggested that injury to inhibitory (suppressor) areas might be especially epileptogenic, since this might result in a removal of some degree of normal inhibition from all areas with neuronal

connexions from the damaged area. However, the evidence is not convincing. Moreover, the argument might be applied, *mutatis mutandis*, to the production of akinetic or inhibitory attacks from damage to areas mainly excitatory. As may be seen from Fig. 2, there are areas of wounding where the incidence of epilepsy is high and others where it appears low, but statistical analysis reveals only a random distribution of positive and negative wounds. One point does however clearly emerge from this analysis, though its meaning is not very apparent. Wounds lying within 5 cm. of the sagittal line are charted in the halo of the skull outline, and they are found to have a much lower incidence of epilepsy than the wounds charted within the main outline. The figures are given in Table VI. The difference is highly significant ($P < \cdot 001$). It is possible that this also may reflect an anatomical factor, and the question will be considered further in a later section.

TABLE VI

INCIDENCE OF EPILEPSY IN WOUNDS OF MEDIAL AND LATERAL PARTS OF HEMISPHERES *

	Within Skull Outline	In Halo
Total	379	252
Wounds with fits ..	214 (56%)	92 (35%)

* Table prepared from Fig. 2.

By way of contributing to the anatomy and physiology of various brain regions, the sections which follow are devoted to analysis of the various types of epileptic phenomena which were observed to occur spontaneously in this series of cases. It is hoped that these studies of spontaneously occurring fits will make some addition to the knowledge gained by other workers (Foerster and Penfield, 1930; Penfield and Erickson, 1941) whose attention has been perhaps specially devoted to the effects of electrical stimulation of the brain at operation in these cases.

Summary

A five-year follow-up of 820 cases of brain wounds from the 1939–45 war is reviewed from the standpoint of traumatic epilepsy, and as an introduction to more detailed studies of groups of cases which will follow.

Overall incidence of epilepsy and the time of onset of first fit after wounding where known, are given for this series. Incidence is already over 43% five years after wounding. This figure, despite great improvements in surgical technique and the avoidance of sepsis, is about the same as was reported from the 1914–18 war cases, and it is therefore suggested that progressive gliosis and scarring *per se* cannot provide an adequate explanation for the occurrence of traumatic epilepsy.

Figures showing the wide variations in the individual case of the frequency of fits are given.

The incidence of epilepsy in wounds of different areas of the brain and of varying severity are compared.

The possible " causes " of traumatic epilepsy are discussed in relation to anatomical and physiological mechanisms.

Acknowledgments will be made in a later section of this study.

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WOUNDS OF THE VISUAL PATHWAY

PART I: THE VISUAL RADIATION

BY

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The representation of the visual field in the visual radiation has received comparatively little attention. In reporting cases of head injury in the first world war, Holmes (1918) stressed the frequency of precise quadrantanopia in wounds of the visual radiation and suggested, though tentatively, that there might be an anatomical interval between the lower half of the radiation subserving the upper quadrant of the visual field and the upper half subserving the lower quadrant. Anatomical studies in monkeys and man have shown, however, that this apparent interval is occupied by fibres subserving central vision which, as elsewhere in the visual pathways, are extremely numerous compared with the area of the visual field they subserve (Polyak, 1934, 1942). Polyak has shown that in the posterior part of the radiation the fibres of central vision separate completely the fibres of peripheral vision which lie above and below them, but in his investigations he apparently examined only the posterior half of the radiation, and Walker and Fulton (1938) have found that in the chimpanzee the anatomy of the anterior radiation is quite different. The present paper reports the defects in the visual field which follow injuries to the radiation in man and describes the anatomical deductions which can be made from them with particular reference to the anterior half of the radiation.

Material

The material is taken from a series of 958 cases of penetrating head injuries, mainly gunshot wounds. One hundred and eighty-eight of these had defects in the visual field attributable to injury to the visual radiation or striate cortex, and this paper is concerned with the 62 cases in which there was a lesion of part of the visual radiation. Cases with severe lesions causing complete or almost complete hemianopia were excluded. The aspects of the cases mentioned in the text are those which are immediately relevant, and case histories are given in the appendix.

The visual fields were plotted with 3/330 and 2/2000 white isopters and also in abnormal areas with 20/2000 white isopter. The interval between injury and examination is shown on each chart.

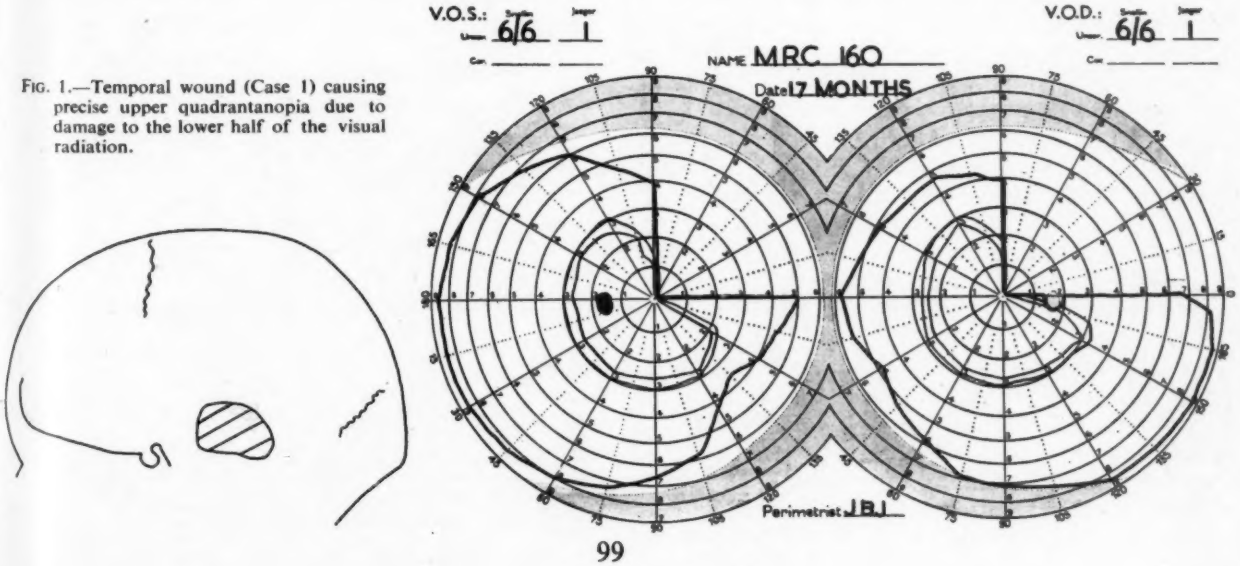


FIG. 1.—Temporal wound (Case 1) causing precise upper quadrantanopia due to damage to the lower half of the visual radiation.

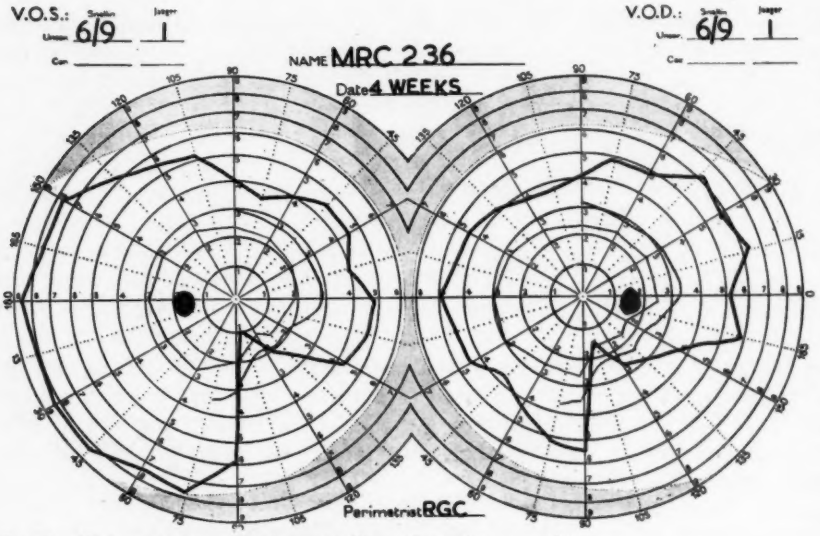


FIG. 2.—High posterior parietal wound (Case 2) causing a partial lower quandrantanopia with sparing of the horizontal meridian and a projection toward the fixation point in the vertical meridian; attributable to damage to the upper margin of the anterior radiation.

In the tracings of radiographs a coarsely hatched area indicates a bony defect in the skull and dense black a radio-opaque foreign body.

Precise quadrantanopia occurred, of which Case 1 (Fig. 1) is an example, but it was the cases with field defects of less than one quadrant that have been of particular interest. The most characteristic field defect is a partial quadrantanopia as illustrated by Cases 2 and 3 (Figs. 2 and 3) in which the striking features are that the horizontal meridian is spared and in the vertical meridian the defect projects towards the fixation point. The site of injury in quadrantic and partial quadrantic field defects is considered in detail below, and it is sufficient to mention here that these two cases are typical, for that with a defect in the lower quadrant received a parasagittal parietal wound, that with a defect in the upper quadrant, a temporal wound. It is impossible to give a precise estimate of the frequency of defects of this type, for they are difficult to assess in the relatively slight cases (Case 4, Fig. 4), but they forced themselves on my attention at a time when their explanation was quite unknown to me. They have moreover been reported before, though without explanation of their shape, and Fig. 5 shows a very characteristic example taken from the first illustration in Cushing's paper (1921) on visual field defects in temporal lobe lesions. Other examples may be found in this and other papers, but this has a particular interest not only because it was one of the earliest of such cases to be recognized (1910), but also because it was the case which enabled Meyer to draw Cushing's attention to the fact that the lower margin of the visual radiation "plunges far forward in the temporal

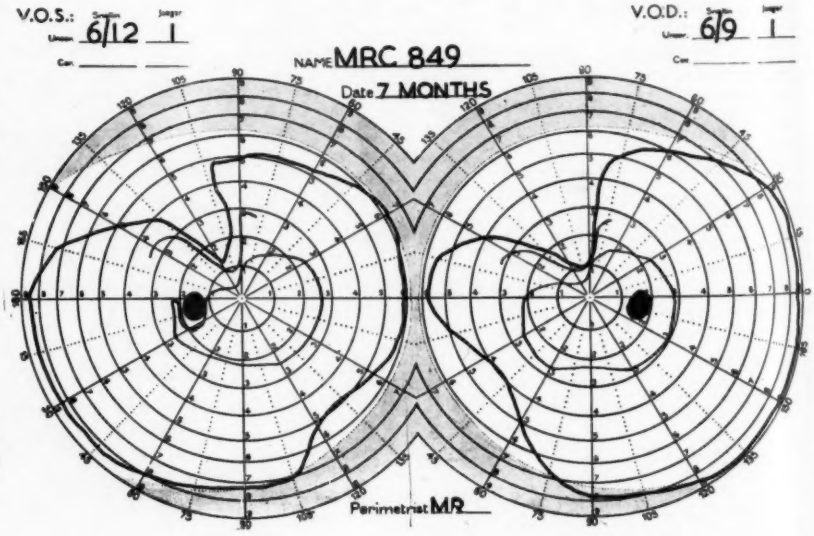
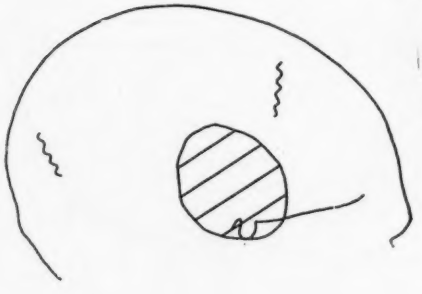


FIG. 3.—Temporal wound (Case 3) causing a partial upper quadrantanopia with sparing of the horizontal meridian and a projection toward the fixation point in the vertical meridian; attributable to damage to the lower margin of the anterior radiation.



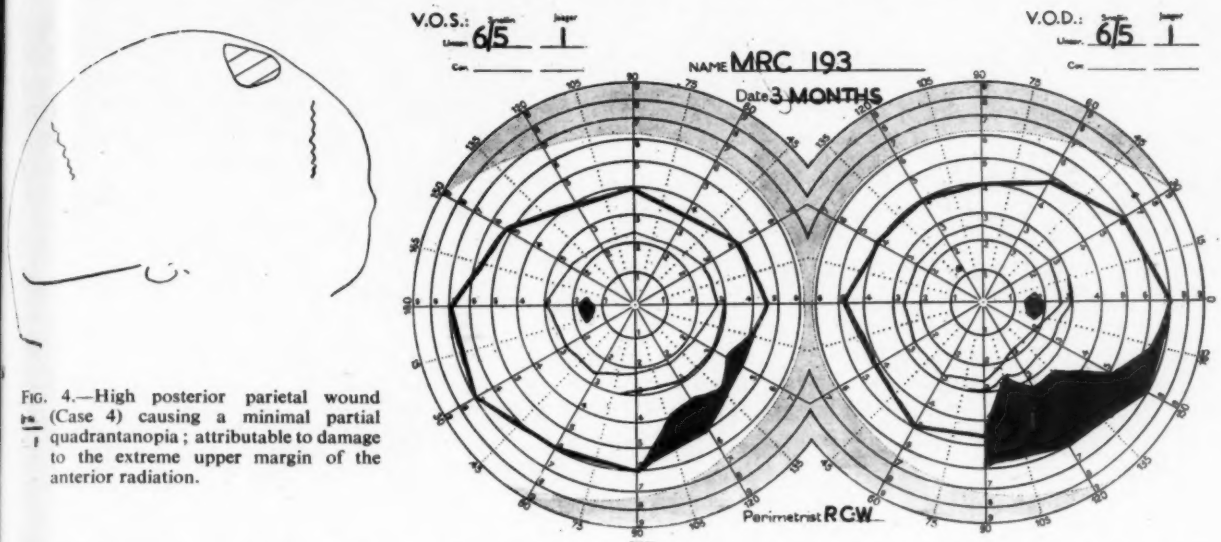


FIG. 4.—High posterior parietal wound (Case 4) causing a minimal partial quadrantanopia; attributable to damage to the extreme upper margin of the anterior radiation.

lobe to sweep around the horn of the ventricle".

The other and more striking field defect is that shown in Case 5 (Fig. 6). It is a narrow, sector-shaped defect in the horizontal meridian involving part of both quadrants and reaching to the fixation point. It is a rare defect occurring in only four cases in this series.

It is clearly important to relate the site of injury in these four cases to the site of injury in other cases of injury to the visual radiation, and this was done by plotting the site of injury in all cases on to a single skull outline by the method described by Russell (1947).

In Fig. 7 are shown the sites of injury in wounds involving the upper part of the radiation (U), the lower part of the radiation (L), and in wounds causing sector-shaped defects (S) of the type shown in Fig. 6. The cases of wounds to the upper

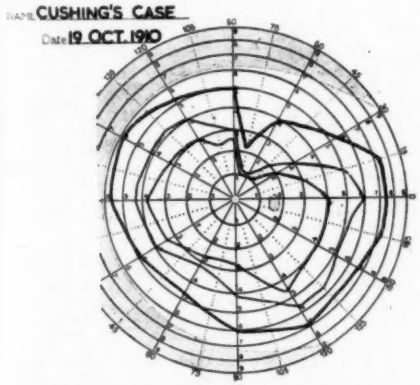


FIG. 5.—From Cushing (1921): partial quadrantanopia in a case of penetrating injury of the temporal lobe, with sparing of the horizontal meridian and a projection toward the fixation point in the vertical meridian; attributable to damage to the lower margin of the anterior radiation.

radiation are selected because the wounds are small. This was necessary to exclude, for instance, wounds involving a large part of the anterior half of the brain but appearing in this series because they extended backwards far enough to involve the upper margin of the visual radiation. The cases indicated by "U" in Fig. 7, therefore, include all cases of wounds of the visual radiation which showed partial or complete lower homonymous quadrantanopia and in which the post-traumatic amnesia was less than 24 hours. The last provision assured that the wound was relatively localized. Cases of injury to the lower radiation are less common than those of the upper, and to exclude cases with post-traumatic amnesia over 24 hours would unduly reduce the total number. The five cases with injuries to the eye penetrating backwards into the temporal lobe were excluded, as were one case with two wounds and one for which there is no satisfactory radiograph available. The remainder comprise the cases indicated with an "L" in Fig. 7, and with the above exceptions represent all cases of wounds of the radiation causing a complete or partial upper quadrantanopia. It should be emphasized that the cases of injury to the upper and lower radiation were selected in accordance with the criteria mentioned above, and that *all* cases which fulfilled the necessary qualification are included in Fig. 7.

It is plain that narrow, sector-shaped defects in the horizontal meridian are due to lesions of the intermediate part (that is, the part lying midway between the upper and lower margins) of the visual radiation in its anterior part. Case 5 (Fig. 6) shows that they are due to a lesion in the whole horizontal thickness of that part of the radiation, for the

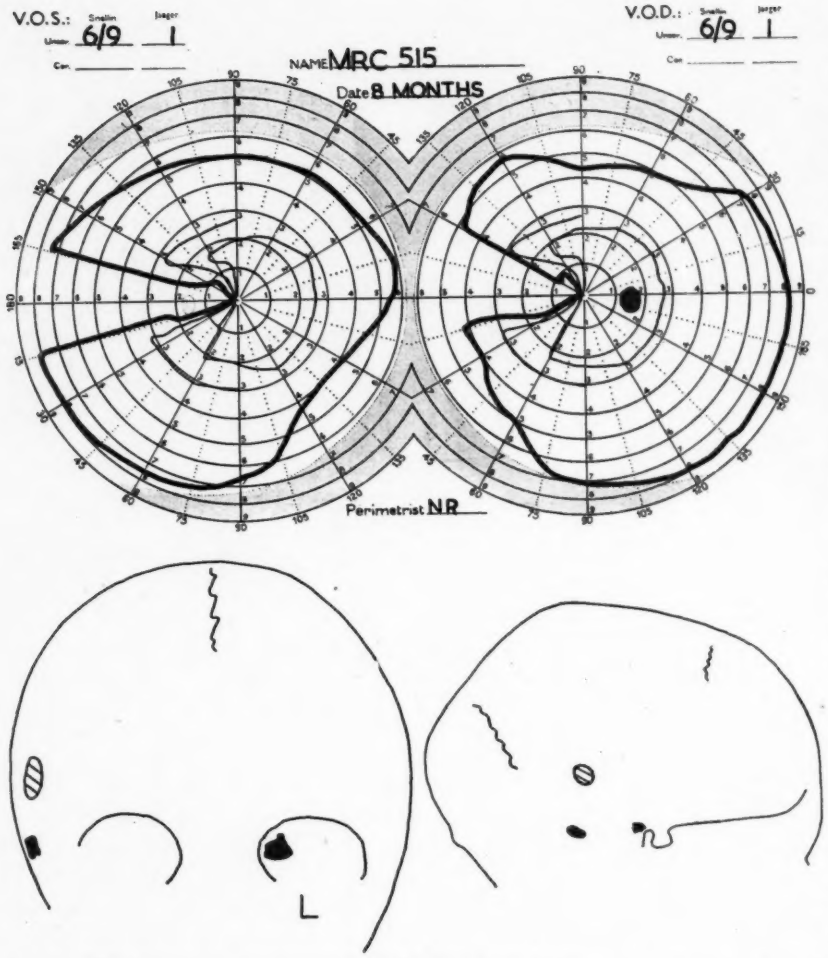


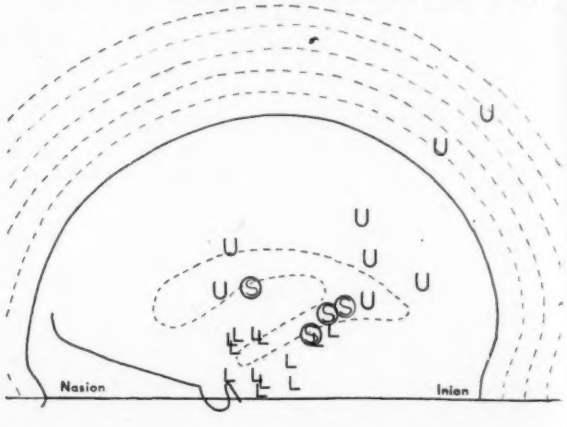
FIG. 6.—Right temporo-parietal wound (Case 5) with a foreign body crossing the mid-line, causing a sector-shaped defect in the horizontal meridian reaching to the fixation point; attributable to damage to the intermediate part (i.e., neither upper nor lower margin) of the anterior radiation.

foreign body which is indicated on the side opposite to the site of entry passed right through the radiation. We have, therefore, to find an explanation for these phenomena, namely: (1) sector-shaped defects in the horizontal meridian of the visual field due to lesions of the intermediate part of the anterior radiation; (2) partial quadrantanopia sparing the horizontal meridian and projecting towards the fixation point in the vertical meridian due to a lesion of the upper or lower margin of the anterior radiation.

These phenomena indicate the anatomical relationship of fibres in the visual radiation, but before considering this it is necessary to review the shape and relations of the visual radiation. Fig. 8a shows the visual radiation as it fans out from the lateral geniculate body round the anterior aspect of the trigone of the ventricle and the anterosuperior aspect of the temporal horn and passes back along the lateral aspect of the ventricle to reach the striate cortex.

The lines I and II in Fig. 8a indicate two planes, through the trigone and through the posterior horn of the ventricle respectively. Fig. 8b shows a coronal section in plane I of the left cerebral hemisphere seen from behind. The visual radiation forms a relatively flat plate on the lateral aspect of the trigone. Fig. 8c shows a similar section in plane II. The visual radiation turns medially at its upper and lower margins so that in this plane it appears as a horseshoe-shaped structure embracing the posterior horn of the ventricle. From the two ends of the horseshoe the visual radiation enters the anterior part of the striate cortex. Fig. 9 shows in diagrammatic form the right visual half-field (a), left lateral geniculate body (b) and the left visual radiation in planes I (c) and II (d), and the representation of the visual field in these structures. The left lateral geniculate body is sectioned about the

FIG. 7.—Sites of injury in wounds involving the upper part of the radiation (U), the lower part of the radiation (L), and in wounds causing sector-shaped defects (S) of the type shown in Fig. 7.



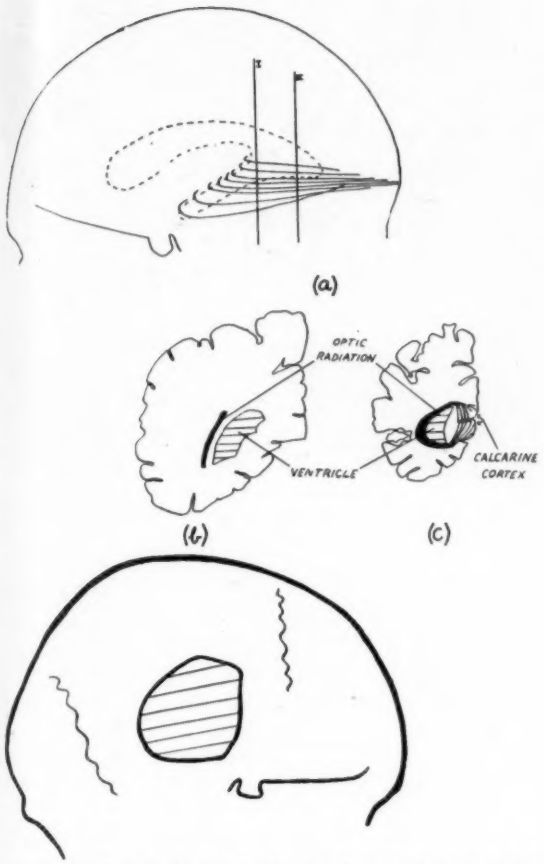


FIG. 8.—(*a*) Visual radiation fanning out from the lateral geniculate body and passing back along the lateral aspect of the ventricle. Plane I through the trigone of the ventricle, plane II through the posterior horn. (*b*) Coronal section, seen from behind, of the left cerebral hemisphere in plane I. (*c*) Similar section in plane II.

middle of its antero-posterior diameter. It is recognized that the level of section alters the appearance of the lateral geniculate body and, in particular, the proportion of the area of cut surface which is devoted to central and to peripheral vision. But for the present purposes neither the differences at different levels of section nor the mode of termination of the optic nerve fibres in the six layers of the lateral geniculate body (Glees and Le Gros Clark, 1941) are important. The anterior visual radiation (c) shows the representation of the visual field necessary to explain the phenomena mentioned above (Fig. 10). The posterior visual radiation (Fig. 9D) shows the representation of the visual field which has been demonstrated by Polyak and others.

Diagrams of this type are notoriously difficult to follow, and therefore the conventions may usefully be explained in some detail. In the visual field the different parts of the upper quadrant are indicated by numbers, the lower by letters. In both quadrants each series runs from centre to periphery so that any one series (e.g., i, ii, iii, 1, 2, 3, or A, B, C) indicates a sector, whereas the corresponding symbols from adjoining series (e.g., ii, II, 2, c, C, γ) indicate an arc of the visual field. Radii dividing the visual field are represented by dotted lines whereas linear arcs are represented by dashed lines.

In the lateral geniculate body (B) central vision is represented in cells lying superiorly, and peripheral vision in those lying inferiorly. The upper quadrant of the visual field is represented laterally, the lower medially, and the horizontal meridian approximately vertically. In the anterior radiation the orientation of fibres has turned anti-clockwise

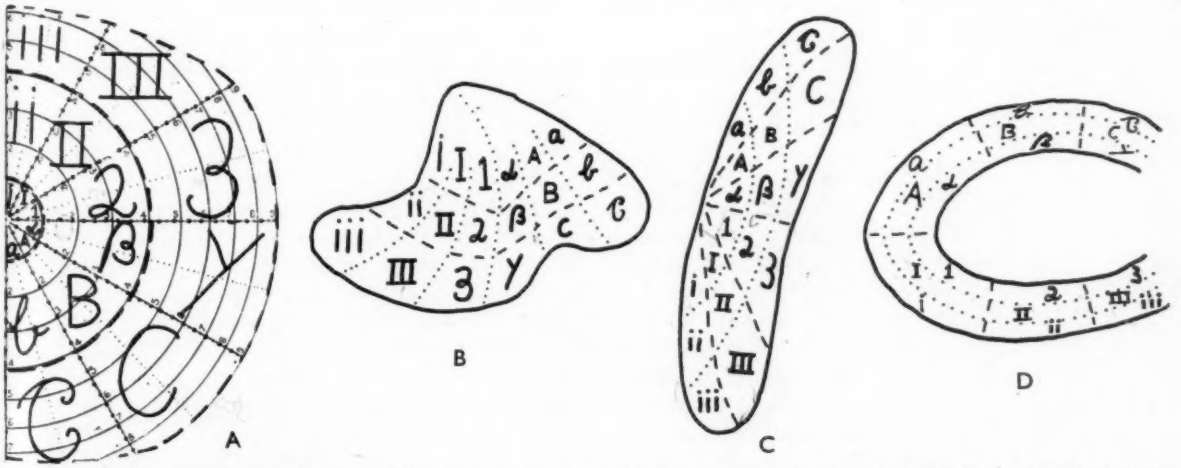


FIG. 9.—(A) Right visual half field, (B) left lateral geniculate body, in corona section seen from behind, (C) left visual radiation in plane I, and (D) in plane II. The representation of the visual field is shown in these structures. Consecutive series (e.g., i, ii, iii, 1, 2, 3, or A, B, C) indicates a sector, and corresponding symbols from adjoining series (e.g., ii, II, 2, c, C, γ) indicate an arc of the visual field.

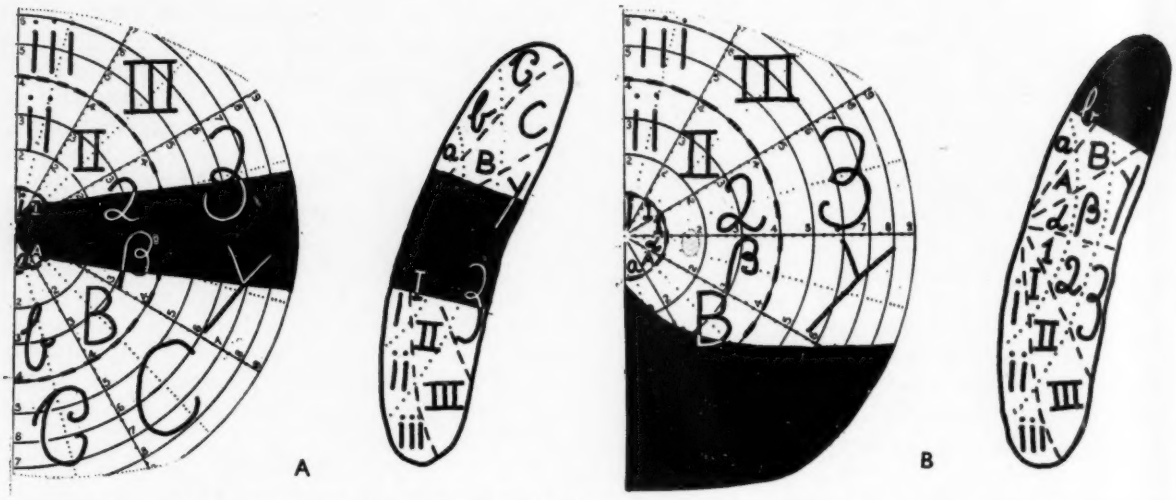


FIG. 10.—Schema showing the effect of lesions of the anterior radiation assuming the representation of the visual field proposed in Fig. 9: (A) lesion of the intermediate part, and (B) lesion of the upper margin.

through nearly a right angle. The fibres representing central vision now lie spread out over a large part of the lateral aspect of the visual radiation though tending to concentrate on its intermediate part, whereas the fibres of peripheral vision are spread out over the medial aspect of the visual radiation tending to concentrate at the upper and lower margins and to thin out over the intermediate part. The horizontal meridian, therefore, is represented more or less horizontally in the intermediate part of the radiation at this point. In the posterior radiation (D) the fibres of central vision have come to occupy the whole of the intermediate part of the radiation and lie lateral to the posterior horn of the ventricle as they pass back to the posterior pole of the occipital lobe. The fibres of peripheral vision have become concentrated at the margins of the radiation, that is, at the two ends of the horseshoe, a position which they must occupy, since in this plane they are already entering the anterior part of the striate cortex.

The suggested arrangement of fibres in the anterior radiation is, therefore, quite compatible with what is already known of the arrangement of the cell bodies of those fibres in the lateral geniculate body and with their course in the posterior radiation.

Briefly, the evidence presented above shows that, contrary to previous beliefs, in the anterior radiation the fibres of central vision are spread out on the lateral aspect of the radiation and tend to be concentrated in the intermediate part, whereas the fibres of peripheral vision are spread out on the medial aspect of the radiation and tend to be concentrated on the upper and lower margins. In the light of this interpretation it is easy to understand why Holmes (1918) found no case of paracentral scotoma due to a wound of the visual radiation in the first world war. For a wound of the anterior radiation that caused such a scotoma would have to involve the intermediate part of the radiation in only half its thickness, and a wound of the posterior radiation that involved the fibres of central vision would be separated by little more than the posterior horn of the ventricle from the remainder of the radiation and from the striate cortex. The chances of such an injury occurring are extremely slight. Because of its rarity and because it is of interest in view of the above remarks, a case of paracentral scotoma due to a wound of the anterior radiation is shown. This man (Case 6) received rather a large right temporo-parietal wound (Fig. 11), and in the acute stage was thought on confrontation to have a complete left homonymous hemianopia. Twenty-five days after injury, when he was first fit to be fully tested, the visual fields showed a wide sector-shaped defect above and below the horizontal meridian. Nineteen months after injury he had improved markedly and had only a small triangular paracentral scotoma running along and just below the horizontal meridian. It is submitted that the site of injury combined with the wide sector defect at 25 days indicate an injury to the anterior radiation, and that the scotoma is evidence of permanent damage confined to the lateral part of the intermediate section of the anterior radiation.

Discussion

This investigation is based on a series of 62 cases of injury to the visual radiation by wounds, mainly gunshot, which penetrated the dura mater. As

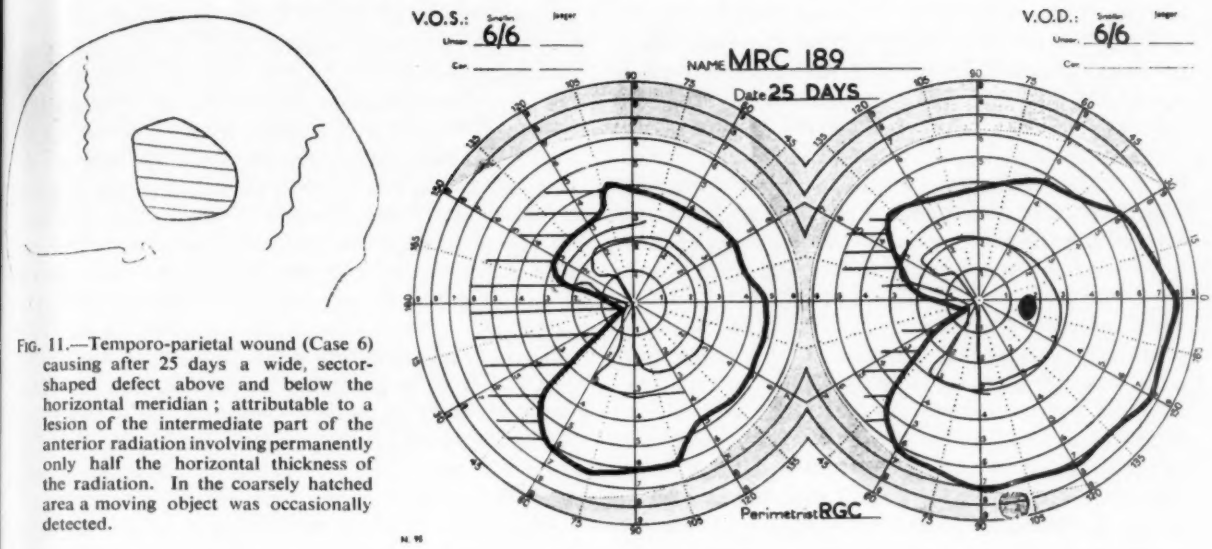
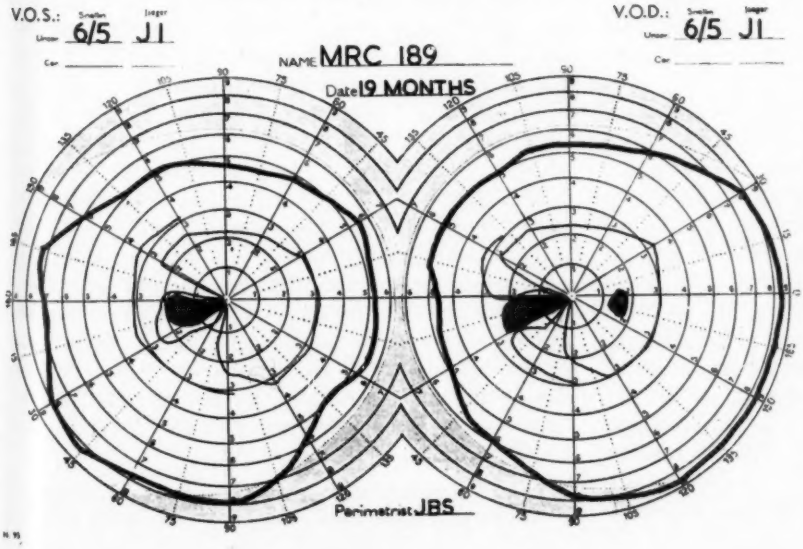


FIG. 11.—Temporo-parietal wound (Case 6) causing after 25 days a wide, sector-shaped defect above and below the horizontal meridian; attributable to a lesion of the intermediate part of the anterior radiation involving permanently only half the horizontal thickness of the radiation. In the coarsely hatched area a moving object was occasionally detected.

well as the cases with precise quadrantanopia which the experience of the first world war had led us to expect, defects also occurred in the visual field which involve less than a complete quadrant and they fall into two clearly distinguishable categories. The commoner is that in which part of one quadrant is affected and in which the horizontal meridian is spared and in the vertical meridian the field defect projects towards the fixation point. These are referred to below as "partial quadrantanopias". The other and much rarer type of defect in the visual field is the narrow, sector-shaped defect in the horizontal meridian.

Partial quadrantanopia has been reported before (Cushing, 1921), and the present series confirms the previous view that partial quadrantanopia in the upper quadrant occurs in lesions of the lower margin of the visual radiation in its anterior (temporal) part; that is, in lesions of Meyer's loop (Meyer, 1907). Similarly partial quadrantanopia in the lower quadrant is due to a lesion of the upper margin of the visual radiation in its anterior part.

Sector-shaped defects in the horizontal meridian, on the other hand, have not previously been recognized as a possible sequel of a lesion of the visual radiation, and indeed Polyak (1942) specifically denies that they can occur in this way, and states that they are always due to a lesion of the striate cortex as in the case described by Holmes (1931). The four cases mentioned above are the only cases with this type of field defect in this series of 188 cases which have injuries involving the visual radiation or striate cortex, and the sites of injury close together in the temporo-parietal region prove that the injury is to the visual radiation not to the striate cortex. Moreover, it is clear that the injury must be to the whole horizontal thickness of the visual radiation, for in the case illustrated (Fig. 5) a foreign body has entered through a relatively small bony defect in the skull and crossed the midline coming to rest in a position which can only have been reached by traversing the visual radiation on the side of entry.



As Fig. 7 shows, the injuries

which produce narrow, horizontal, sector-shaped defects lie intermediately between those which produce upper and those which produce lower quadrantic defects. This type of sector-shaped defect is, therefore, due to injury of the intermediate part of the visual radiation, that is, to that part of the radiation lying midway between its upper and lower margins. Moreover these injuries are anterior to or at the level of the trigone and can properly be presumed to have involved the anterior part of the visual radiation, a part which, unlike its neighbours in the visual system, the lateral geniculate body and the posterior part of the radiation, has received little or no attention from the anatomists.

It has been stated by several authors and most emphatically by Polyak (1942) that the upper part of the radiation is concerned with vision in the lower quadrant of the visual field, the lower part with vision in the upper quadrant and that the intermediate part is occupied by fibres concerned with central vision. This thesis, though put forward as applicable to the whole visual radiation, is based on experimental and clinical material in which apparently only the posterior horseshoe-shaped part (Figs. 8c, 9D) has been examined, and is incompatible with the occurrence of narrow, horizontal, sector-shaped defects of the visual field in injuries of the intermediate part of the anterior radiation. The implication of this type of sector-shaped defect is that in the anterior radiation the peripheral field in the horizontal meridian is represented in the same horizontal plane as is central vision. The arrangement of fibres which will explain the phenomena is that shown in Fig. 9, in which the fibres subserving central vision are spread out over the lateral aspect of the radiation tending to congregate towards the intermediate part, whereas the fibres subserving peripheral vision are spread out on the medial aspect tending to congregate at the upper and lower margin.

This arrangement may be postulated merely from the site of injury in cases of narrow, horizontal, sector-shaped defects, but it receives much support from consideration of the effect of an injury to the upper or lower margin of the anterior radiation. If the proposed arrangement is correct, we should expect a partial quadrantic field defect in which the horizontal meridian is spared and in the vertical meridian the defect projects towards the fixation point (Fig. 10). That is to say, this arrangement of fibres also accounts for the occurrence of partial quadrantic defects which are characteristic in shape and are common both in present and in previous material, but whose aetiology was previously unknown. The sparing of the horizontal meridian occurs because this part of the visual field is represented in the intermediate part of the anterior radiation as is shown by the cases of sector-shaped defect. The projection of the defect towards the fixation point appears because a lesion of the upper or lower margin of the anterior radiation, as illustrated diagrammatically in Fig. 10, will involve a few of the fibres of central vision, and if these fibres are arranged in an orderly manner at all (as they undoubtedly are) the fibres involved will be those of central or pericentral vision in the vertical meridian.

This arrangement of fibres in the anterior radiation is therefore necessary to explain the observed facts. It remains to fit it in with what is known of the anatomy of the lateral geniculate body and the posterior part of the radiation. In the lateral geniculate body (Fig. 9b) central vision is represented superiorly, upper peripheral vision infero-laterally, and lower peripheral vision infero-medially (Brouwer and Zeeman, 1926; Mackenzie, Meighan, and Pollock, 1933; Le Gros Clark and Penman, 1934; Chacko, 1948). The horizontal meridian of the visual field is represented approximately vertically. In the anterior radiation, according to the suggested arrangement, the representation of the visual field follows the same general pattern as in the lateral geniculate body, but the axis of the system is turned through nearly a right angle in an anticlockwise direction. (This refers as before to the left hemisphere seen from behind.) The fibres of central vision thus come to lie on the lateral aspect of the radiation, the fibres of peripheral vision on the medial aspect, and the horizontal meridian is represented approximately horizontally. The fibres of peripheral vision thin out in the intermediate part of the anterior radiation, tending to congregate in the upper and lower margin, and this process continues so that in the posterior radiation peripheral vision is represented in the upper and lower limbs of the "horseshoe" corresponding to the upper and lower margins of the anterior radiation. This arrangement in the posterior radiation has been clearly demonstrated (Putnam, 1926; Brouwer, 1934; Polyak, 1934, 1941, 1942).

The postulated arrangement of fibres in the anterior radiation therefore fits in well with what is known of the anatomy of its neighbours in the visual pathways, the lateral geniculate body and the posterior radiation. It is moreover in accord with the very scanty evidence on the subject obtained from animal experiment, namely Walker and Fulton's (1938) observation that

> "the degeneration in the lateral geniculate body . . . following the temporal lobe lesion was quite different

from that following an occipital lobe injury. The patchy degeneration of the lateral geniculate body in the first instance probably indicates that the component parts of the visual radiation do not maintain an exact constant relationship throughout their course, and that there is some intermingling of fibres".

We must conclude that there is good evidence in favour of, and none against, the proposition that in the anterior part of the radiation the fibres of central vision are spread out on the lateral aspect of the visual radiation, tending to congregate at its intermediate part, and the fibres of peripheral vision are spread out on the medial aspect, tending to congregate at its upper and lower margins. This also accounts for the extreme rarity of paracentral scotomata in injuries to the anterior radiation though they occur very occasionally as in Case 6 (Fig. 11) above.

Summary

A series of 958 cases of penetrating head injury, mainly gunshot wounds, has been reviewed to determine what light they throw on the anatomy of the visual radiation. In 188 of these there was a visual field defect attributable to injury to the visual radiation or striate cortex, and the conclusions are based on the 62 of these cases in which injury was confined to the visual radiation.

Wounds involving the upper or lower margins of the anterior part of the visual radiation cause partial quadrantanopia in which the horizontal meridian is spared and the field defect projects towards the fixation point in the vertical meridian.

Wounds involving the intermediate part of the anterior radiation cause narrow, sector-shaped defects in the horizontal meridian reaching to the fixation point.

It follows that in the anterior radiation fibres subserving central vision lie on the lateral aspect, tending to congregate at the intermediate part, and fibres subserving peripheral vision lie on the medial aspect, tending to congregate at the upper and lower margins. This arrangement, though contrary to previous beliefs, is in accord with both experimental and clinical evidence.

APPENDIX

Case 1.—M.R.C.160,* a man aged 30, on July 31, 1944, received a left temporal gunshot wound (Fig. 1) with a post-traumatic amnesia between one and three weeks. Thirty hours after injury his wound was excised. The skull defect was found to involve the apex of the mastoid air cells, and there was a cavity the size of a large plum filled with debris in the posterior inferior temporal convolution, with an extension upwards and medially to involve the posterior portion of the temporal horn of the ventricle.

On arrival at the Military Hospital for Head Injuries, Oxford, four days after injury, he was conscious but profoundly aphasic. He was thought to have a right homonymous hemianopia, and had a minimal hemiparesis which cleared up within six weeks. His convalescence was delayed by a chronic "aseptic" meningitis which persisted for five months after injury. An air encephalogram four months after injury showed considerable focal dilatation of the trigone and the whole of the temporal horn of the left lateral ventricle.

It was first possible to examine the visual fields thoroughly about five weeks after injury, when the patient had a complete right upper quadrantic defect. The visual fields were re-examined on several occasions, and on December 20, 1945, 19 months after injury, the complete and precise quadrantanopia persisted (Fig. 1). At this time the patient was able to hold a labouring job, and though he could barely read or write, his dysphasia did not handicap him in his daily life.

Case 2.—M.R.C.236, a man aged 24, on August 11, 1944, received a parasagittal wound in the left posterior parietal region (Fig. 2). Retrograde amnesia was less than 24 hours and post-traumatic amnesia less than a week.

On arrival at the Hospital for Head Injuries the following day he was drowsy, but could be roused, and though he was not obviously dysphasic he could not read. He had, to confrontation, a right homonymous hemianopia with spatial disorientation in the left half field; the right lower limb was very weak, and postural sensation, graphaesthesia, and appreciation of light touch were impaired. There was some increase in the reflexes in both lower limbs and both plantar responses were extensor. Fifty hours after injury the wound was excised, and debris removed from a track running beside the falx to a depth of 6 cm. The most lateral of the bone fragments was left *in situ*.

The patient made a satisfactory recovery, and four months after injury the only abnormal physical signs were considerable impairment of postural sensation in the right toes and the defects in the visual field.

The visual fields were first fully examined three weeks after injury, when they showed a partial quadrantanopia with sparing of the horizontal meridian and a projection towards the fixation point in the vertical meridian. In addition all objects in the right half field appeared blurred and he had difficulty in localizing objects in that half field. The spatial disorientation on the left cleared up entirely. Psychometric tests showed marked incapacity in all tests involving visual imagery or spatial sense.

Case 3.—M.R.C.849, a man aged 24, on April 11, 1945, received a right temporo-parietal injury (Fig. 3) and also wounds of the right side of the chest. There was no retrograde amnesia and post-traumatic amnesia was one or two days. The head wound was caused by a metallic foreign body, which, at operation two days later, was found to have passed downwards and forwards, shattering the zygoma and coming to rest in the right cheek. There was considerable damage to the cerebral cortex, but apparently the temporal horn of the ventricle was not penetrated.

On admission to the Hospital for Head Injuries three months after injury he had a right facial weakness due to partial involvement of the facial nerve in the injury, and a minimal weakness of the left face and arm with slight increase in the reflexes in the left upper and lower limbs, and a flexor plantar response. There was no sensory loss, and the hemiplegia cleared up entirely six months after injury.

Seven months after injury the visual fields showed a left upper partial quadrantic field defect sparing the horizontal meridian and projecting towards the fixation point in the vertical meridian (Fig. 3).

Case 4.—M.R.C.193, a man aged 27, on August 6, 1944, received a parasagittal wound in the left posterior parietal region (Fig. 4). Retrograde amnesia was only a few seconds and post-traumatic amnesia five to 10 minutes.

On arrival at the Hospital for Head Injuries two days later he was alert and well orientated. He had no dysphasia. There was slight weakness of the right upper and of both lower limbs with slight increase in the reflexes in the right upper and lower limbs. Both plantar responses were, however, flexor, and there was no disturbance of any modality of sensation.

At operation, 60 hours after injury, the wound was excised and the dural defect found to measure 3 × 2 cm. Pulped brain and some relatively superficial foreign bodies were removed from the track which penetrated

* Reference number of the M.R.C. Penetrating Head Injury File, Military Hospital, Wheatley, Oxford.

for 4 cm. The patient made a good recovery and was left with no abnormal signs except the visual field defect.

Before operation he was thought, to confrontation, to have a right homonymous hemianopia, possibly not reaching to the fixation point. Two weeks after the injury the fields were first fully examined, and showed an almost complete right lower homonymous quadrantanopia with 10° sparing around the fixation point in the vertical meridian rising to about 20° in the horizontal meridian. The visual fields continued to improve so that three months after injury there was only a slight defect in the periphery of the right lower quadrant sparing the horizontal meridian (Fig. 4).

Case 5.—M.R.C.515, a man aged 33, on November 24, 1944, received a gunshot wound in the right temporoparietal region, and a metallic foreign body crossed the midline coming to rest immediately above and behind the left petrous temporal bone (Fig. 6). Twenty hours after injury the wound was excised, and in addition to the track passing medially caused by the foreign body which crossed the midline, there was a track passing inferiorly with a small laceration in the tentorium. Six days after injury it was necessary to decompress the posterior fossa and to release a tense loculus of cerebrospinal fluid.

On admission to the Hospital for Head Injuries 16 days after injury he was still drowsy and moderately disorientated. There was a slight relative left hemiparesis with exaggerated reflexes in all limbs and bilateral extensor plantar responses. There was dysarthria with gross cerebellar ataxia worse on the left than the right. To confrontation there was thought to be a left homonymous hemianopia. He made an excellent recovery, and eight months after injury he showed a slight left hemiparesis with extensor plantar response on that side and exaggerated tendon jerks in all limbs. There was moderate cerebellar ataxia. The visual field showed a narrow, sector-shaped defect in the horizontal meridian reaching to the fixation point (Fig. 6).

Case 6.—M.R.C.189, a man aged 20, on August 3, 1944, received a gunshot wound low in the right parietal area (Fig. 11), which caused left hemiparesis, hemianaesthesia, and probably hemianopia. At operation 48 hours later there was a rather large bone defect with several fissures running out from it. A considerable amount of brain debris and bone fragments was removed, but the wound did not enter the ventricle.

On arrival at the Hospital for Head Injuries, he was fairly rational and orientated but not able to cooperate well. He had a left hemiparesis, most marked in the face, with impairment of postural sense and appreciation of pin prick on the left side. The hemiparesis improved markedly so that 10 months after injury it was represented only by minimal left facial weakness and slight hyperreflexia in the left upper limb. At that time sensation was normal except for minimal hypalgesia on the left side of the face, minimal astereognosis in the left hand, and slight delay in appreciation of temperature on the left hand.

Five days after injury he was thought to have, on confrontation, a left homonymous hemianopia. Three and a half weeks after injury when first fully examined he had a wide sector defect above and below the horizontal meridian (Fig. 11b), and 19 months after injury he had improved further and had only a left homonymous paracentral wedge-shaped scotoma on and below the horizontal meridian (Fig. 11c).

I wish to express my thanks to Dr. W. Ritchie Russell for his constant help and encouragement. I would also like to thank the surgeons and physicians of the Military Head Injuries Units both at Oxford and in the field for their detailed records, and to the orthoptists, in particular Miss Coates White, D.B.O., for their help with the visual field charts.

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RAPID SERIAL ANGIOGRAPHY: FURTHER EXPERIENCE

BY

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In 1949 a preliminary report on a method of rapid serial angiography of the cerebral vessels was published from this hospital by Curtis (1949). When he returned to Australia we took over the work on this subject, and in this paper we report our observations and an analysis of the serial angiograms which have been made here during the two years in which this method has been used.

Apparatus

A brief description of the machine (Fig. 1) was given in the earlier paper on this subject (Curtis, 1949), and this apparatus has been used for all the cases without modification. It was devised by Dr. E. Schuster and it enables exposures to be made at three variable speeds up to 2 frames per second. Intensifying screens are employed, and the images, each 10 in. wide by 8 in. long, are projected on to a strip of film 20 ft. in length.

An antero-posterior projection has been obtained by rotating the head, but this is unsatisfactory because it is difficult to get accurate alignment, and the lateral projection only is in general use. This has been found to be adequate for most purposes when supplemented by antero-posterior views taken by the standard three-film technique (Curtis, 1951). After injection of the vertebral artery, however, it would be particularly useful if rapid serial angiograms could be taken in the half-axial projection, which provides more information than does the lateral vertebral angiogram. Several models of the machine have been made by Dr. Schuster for other purposes in which this projection is required, and it would be a relatively simple matter to adapt one of these for cerebral angiography.*

There are one or two minor disadvantages, of a technical nature, which depend on the difficulty of developing a long strip of film. As was described in the preliminary report (Curtis, 1949), the film is wound on to a spiral holder of a type similar to that used for aerial photography. Owing to the impossibility of winding wet film back on to the holder once it has been taken off, the process of development, fixation, and washing must be completed before the film is removed. This involves a delay of about an hour before the wet film can be inspected. Apart from the necessity of waiting this time before a diagnosis can be reached, a more serious problem is that the angiogram cannot be repeated on the same occasion if for any reason there should have been a fault in the injection or radiography. Also, in order to study the wet film special fixtures for viewing it are necessary. These are usually not available in the operating theatre, so that if the film is required for immediate exhibition during an operation a further delay is caused.

Irradiation

We have considered the possibility that the amount of irradiation received as a result of a large number of rapidly repeated exposures might be harmful to the patient. By means of accurate measurements the dose has been found not to exceed 20·8r for the maximum number of exposures, which is 25 per film. In practice such a large number of frames is seldom necessary, since most of the contrast has usually passed through the cerebral vessels in eight seconds* as will be shown (Fig. 2). The machine can be stopped automatically after any given number of exposures. The procedure may therefore be repeated once with safety should it be necessary, and if the likelihood of this is envisaged a short film can be taken.

These measurements serve nevertheless to emphasize the need for really efficient protection of the operators, particularly the person responsible for making the injection. A wide curtain of lead-rubber sheeting 1 mm. thick has been found adequate, and with this the maximum dosage for the operator is 0·005r during 25 exposures.

* Messrs. General Radiological Limited hope to manufacture a unit base on a later design by Dr. Schuster in collaboration with the Nuffield Institute for Medical Research. This model is intended for general use but is readily adaptable for cerebral angiography in any projection; it was exhibited at the Sixth International Congress of Radiology in 1950.

* Throughout this paper circulation times quoted have been measured from the beginning of the injection.

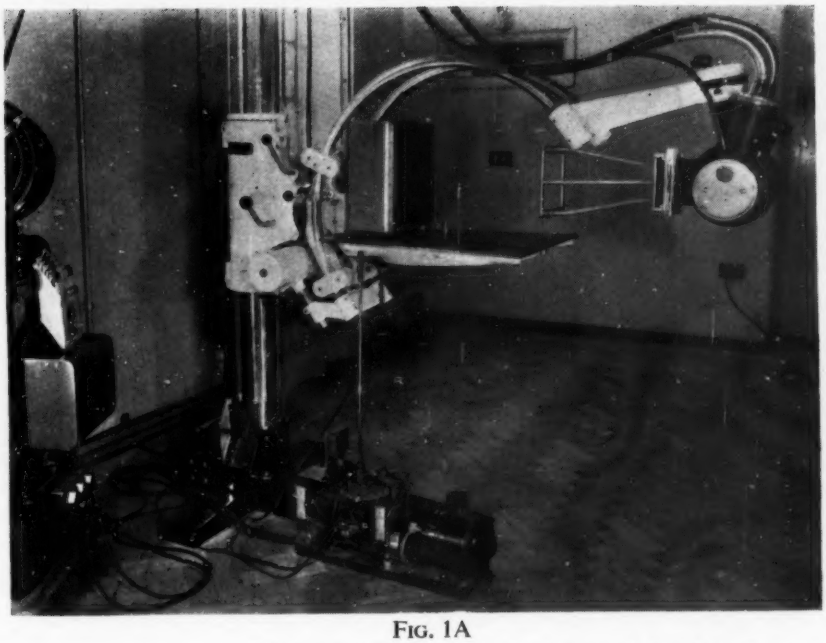

FIG. 1.—A. Rapid serial angiographic apparatus. The power unit is seen below, with a connecting rod leading to the cassette mounted on a Lysholm-Schönander table. The exposure, the spool drive, and the movable intensifying screens are synchronized and operated electrically. The protecting screens and table have been removed for greater clarity.

B. Closer view of power unit. (1) motor; (2) automatic brake and device for altering the pre-set number of exposures; (3) gear lever; (4) electromagnet, operating (5) clutch; (6) starting switch.

FIG. 1A

Case Material

The material consists of 109 serial angiograms from 74 patients. Twenty-one of these angiograms were considered to be within normal limits. The diagnoses of the cases reviewed are analysed in Table I. In a recent paper Curtis (1951) mentioned his observations on some of these films.

Serial angiography is as a rule only employed in those cases in which it is expected that more information will be obtained than by the standard technique. Economy also dictates careful selection, as the cost of a full film of 25 exposures is seven times that of the film used in the standard technique. In the six-month period, October, 1950, to March, 1951, 131 angiographic examinations were made at the Radcliffe Infirmary, for which the rapid serial method was employed in 19.

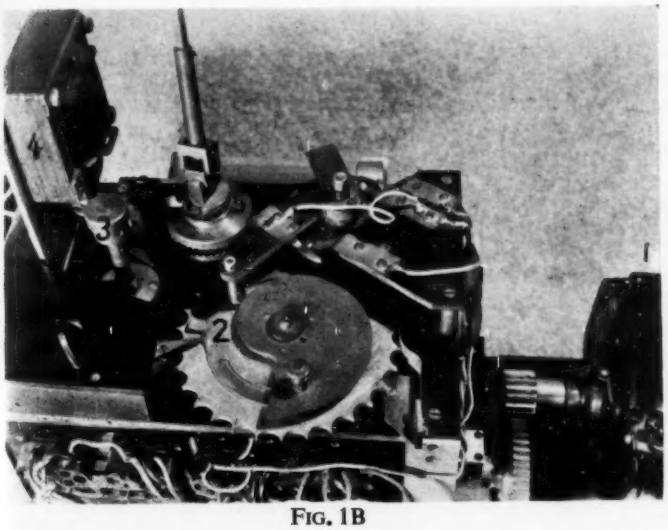

FIG. 1B

We intend to discuss only those points which have arisen as a result of our study of the serial angiograms taken in the last two years, as the more general aspects of the subject have been frequently described elsewhere.

The Normal Cerebral Circulation

The "normal" material consists of those angiograms in which no displacement of vessels or other abnormality was visible in any part of the film, and in which the diagnosis of the case was such that we did not consider it likely that the part of the circulatory system being studied was affected to any significant extent by the disease process (Table II).

Variations in Circulation Time.—In order to facilitate comparison, the circulation times in the 21 normal cases have been tabulated diagrammatically in Fig. 2. The most striking feature will be seen to be the large variation between the cases. When the durations of the venous phases are compared it is seen that these varied in length from two seconds to more than nine and a half seconds. The arterial phases were more consistent and varied from one and one third to three and one third seconds.

Of course, the cerebral circulation is influenced in many ways by present methods of angiography; it is not, therefore studied under physiological conditions. The main technical factors which may affect the record of the circulation that is obtained are as follows.

TABLE I
CASE MATERIAL

Description of Case	No. of Cases
Normal (carotid)	20
Normal (vertebral)	1
Glioblastoma multiforme	11
Astrocytoma	3
Oligodendroglioma	2
Meningioma	4
Secondary neoplasms	5
Arteriovenous malformations	9
Aneurysms—various	7
Thrombosis	5
Miscellaneous	7
Total	74

TABLE II
DIAGNOSES OF CASES WITH "NORMAL" ANGIOGRAMS

Case	Diagnosis	Case	Diagnosis
1	Focal epilepsy	11	Focal epilepsy
2	Otitic hydrocephalus	12	Secondary carcinoma in cerebellum
3	Thrombosis in opposite hemisphere	13	Cerebral arteriosclerosis
4	Subarachnoid haemorrhage	14	Focal epilepsy
5	Meningitis (pyogenic)	15	Migraine
6	Penetrating parietal injury	16	Senile cerebral degeneration
7	Subarachnoid haemorrhage	17	Migraine
8	Subarachnoid haemorrhage	18	Focal epilepsy
9	Suspected tumour	19	Focal epilepsy
10	Thrombosis in opposite hemisphere	20	Focal epilepsy
		21	Subarachnoid haemorrhage

The Puncture.—The size of the lumen of the needle influences the rate at which the contrast substance can be injected, and the site at which the needle is inserted into the carotid system makes a considerable difference to the angiogram obtained. If the injection is made into the internal carotid artery, all the contrast substance is delivered into the cerebral circulation. If, on the other hand, the injection is made into the common carotid artery, the proportion of contrast medium which is distributed between the external and internal carotid circulations is variable. The predominant course taken by the opaque fluid is governed to some extent by the direction in which the bevelled end of the needle is pointed. The flow of the contrast substance is also impeded if the needle does not lie fully within the lumen of the vessel, and we have omitted cases from consideration in which doubt existed about the freedom of flow through the needle. If the puncture is difficult the artery may be compressed by extravasated blood or put into spasm, and direct stimulation of the carotid sinus is also a possibility.

The Contrast Substance.—We have no accurate details of the action of diodone*, which was the contrast substance used in all these cases, on the cerebral blood vessels. The flushing of the face, often preceded by transient pallor, and injection of the conjunctiva, are well known effects on extracerebral vessels. There is possibly some stimulation of perivascular autonomic fibres since the injection is frequently associated with pupillary dilatation.

The contractility of pial vessels has been established (Florey, 1925 ; Forbes and Wolff, 1928) and the intracerebral arteries may be expected to be affected in a similar manner to those of the extracerebral circulation. The duration of this influence may be such as to affect the circulation time when contrast substance is injected twice at the same session, but we have insufficient material to draw any definite conclusions on this point. In three cases, however, in which the serial examination was repeated after a short interval (about 20 minutes), no significant differences in the circulation time were demonstrated. The only means of demonstrating any direct influence of the contrast substance on the circulation time would be to compare a number of angiograms in which two injections were given : for the first injection a non-irritant substance would be employed, and for the second, diodone. The only non-irritant contrast medium available at the present time is thorotrast, and we have not felt justified in using this because of its possible harmful effects.

The Injection.—The main factor affecting the duration of vascular filling is the time occupied by the injection ; this of course depends on the volume of contrast substance and the speed of injection. The volume given to adults in our series was usually 10 or 12 ml., depending on the length of rubber tubing attached to the syringe, and the time occupied by the injection was about two seconds in all our cases. As the first frame is taken at the moment the injection is begun, it is possible to measure this time in the serial films by noting the disappearance of the column of contrast from the neck. The rate of injection evidently affects pressure relationships within the Circle of Willis, and on account of this some vessels occasionally take up contrast at the expense of others. We have found that when the anterior cerebral artery has failed to fill it has sometimes been due to too rapid injection of the contrast substance. Obviously, the volume injected will also influence the circulation time, and the shortest in our series (Case 2) occurred in a child aged 3 years, in whom an injection of only 6 ml. of contrast was used.

Other Factors.—The wide variations in the normal circulation time cannot be entirely explained by the technical factors of the injection, and, although conditions are manifestly far from physiological during angiography, we feel justified in concluding

* Pyelosil, Glaxo.

that the normal circulation time is subject to considerable variation. This is probably due partly to differences in pulse rate, pulse volume, and blood pressure. These factors may in their turn be influenced by the procedure to some degree: the patient will often be more or less upset by the investigation, with resulting increase in the pulse rate and consequently a more rapid circulation time. As shown by Curtis (1951), the blood pressure may be raised after injection of diodone into the carotid arteries. As a further cause of variations among apparently normal circulation times, the possibility of arteriovenous or intervenous anastomotic channels in the brain, similar to those described in the kidney (Trueta, Barclay, Daniel, Franklin, and Prichard, 1947) and liver (Daniel and Prichard, 1951), should also be considered.

The Circulatory Phases.—We find that there is no direct proportion between the length of the arterial phase and that of the venous phase (Fig. 2). The capillary phase was seen in comparatively few serial angiograms with frames at intervals of $\frac{2}{3}$ second. This apparent overlap of the various parts of the sequence is presumed to be partly due to the volume of the contrast substance, but another important point is that the capillary phase may not take place over the whole brain at the same moment. These remarks are not fully in agreement with the views of Moniz (1940), but some differences may be due to the fact that he used thorotrast for his injections. We do not therefore feel that it is possible at the present time to draw any hard and fast conclusions about the duration of the phases of the cerebral circulation. It will be appreciated that it is impossible to get a film of any particular phase, other than the arterial one, with any degree of reliability using only three frames.

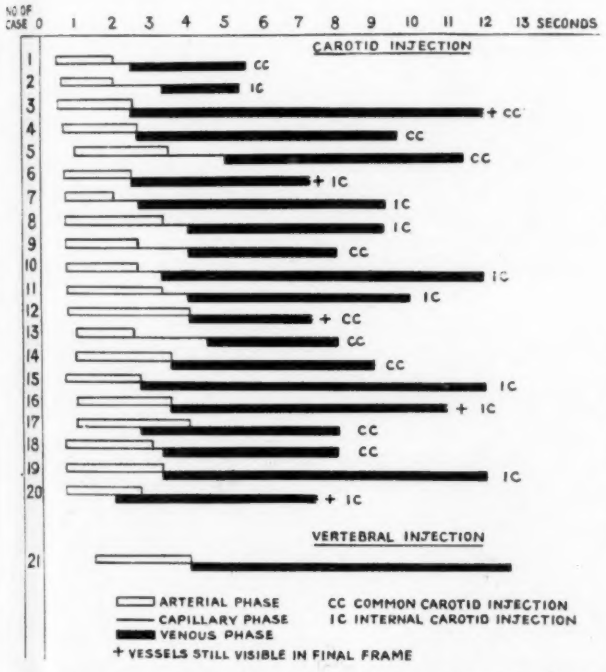
NO OF CASE
0 1 2 3 4 5 6 7 8 9 10 11 12 13 SECONDS
CAROTID INJECTION
VERTEBRAL INJECTION
ARTERIAL PHASE
CAPILLARY PHASE
VENOUS PHASE
+ VESSELS STILL VISIBLE IN FINAL FRAME
CC COMMON CAROTID INJECTION
IC INTERNAL CAROTID INJECTION

FIG. 2.—Circulation times in 21 normal serial angiograms. About 10 ml. diodone (allowing for the volume within the tubing) were injected for each angiogram, except in Cases 2 (6 ml.), 5, and 12 (8 ml.). Cases 2 and 17 were examined under general anaesthesia. Case 2 was 3 years old, the remainder were adult (19–52 years). The inferior longitudinal sinus is not included in measurements of the venous phase. The complete angiogram of Case 10 was illustrated in the preliminary report (Curtis, 1949).

The Sequence of Venous Filling.—Curtis (1951) stated that in the venous phase "the deep cerebral veins and certain superficial veins around the anterior part of the temporal lobe and Sylvian point are the first to be seen". This was true in 15 of our 20 normal serial carotid angiograms, but in the remainder the inferior longitudinal sinus was the first venous channel to be seen. In some films it appeared during the arterial phase when the arteries were still well filled by the contrast substance. The relationship of filling of the inferior longitudinal sinus to the filling of the other superficial and deep veins is shown in Fig. 3. It is a curious fact that in 10 of the 20 cases this sinus was not visible at any stage.

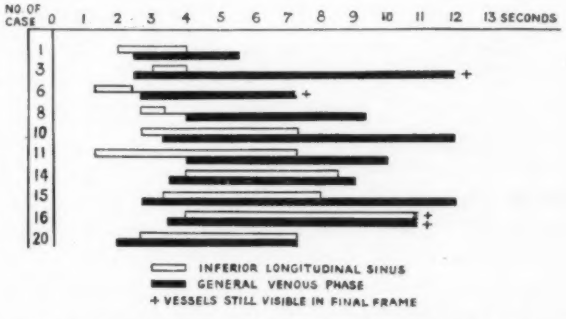
NO OF CASE
0 1 2 3 4 5 6 7 8 9 10 11 12 13 SECONDS
INFERIOR LONGITUDINAL SINUS
GENERAL VENOUS PHASE
+ VESSELS STILL VISIBLE IN FINAL FRAME

FIG. 3.—The duration of filling of the inferior longitudinal sinus has been compared with that of the remainder of the cerebral venous channels. The sinus was visible in 10 cases out of 20, and was the first venous channel to appear in five cases out of 10.

The deep (internal) cerebral veins are usually seen to fill in the same frame as the superficial cerebral veins, or often a little later (Fig. 4).

Our experience does not confirm Curtis's statement (1951) that the deep veins are usually the first to empty. In our 20 cases they emptied first in three, last in five, and in the others at about the same time as the superficial veins or at a time which was indeterminable on account of the presence of contrast in both sets of veins in the last frame (Fig. 4).

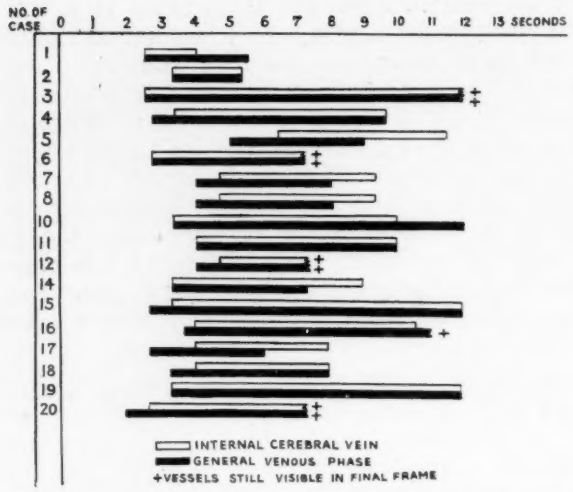

FIG. 4.—Comparison of the duration of filling of the internal cerebral vein with that of the remaining venous channels, excluding the inferior longitudinal sinus. Cases 9 and 13 are omitted because the internal cerebral vein was not sufficiently clearly seen in these angiograms to allow conclusions to be drawn. This vessel appears at the same time, or just after the other venous channels, and in the 14 cases in which it can be followed through it disappeared first in three, last in five, and together with the remaining vessels in six.

The Choroidal Plexus of the Eye

During the study of these rapid serial angiograms a crescentic line was observed within the orbit produced by contrast substance in the choroidal plexus of the eye (Schurr, 1951). This appearance was found in 11 of the 20 normal carotid angiograms, and it was visible between the average times of two and five and a half seconds (Fig. 5). It is probably produced mainly by venous channels, since it usually begins to appear when the ophthalmic artery is fading, and it remains for about half the duration of the venous phase of the cerebral circulation. The contrast seems to appear first at a point just above the meridian of the globe. It develops as a fine crescent with clear outlines, and then gradually fades away. Pathological appearances of the choroidal plexus have not yet been studied, but it is possible that a technique could be developed which would be of use in the demonstration and differential diagnosis of some orbital and ocular neoplasms.

The Pathological Circulation

Tumour Diagnosis.—It is a matter of common experience that it is easier to come to a conclusion about a diagnosis if there are several slightly different films on which to base an opinion than if there are only one or two. In these circumstances a serial film may be a great help. When doubt exists about the presence or absence of a vessel, or whether it is a vein or an artery, the matter can usually be resolved by watching its gradual appearance and disappearance in successive frames of a serial angiogram.

It happens on rare occasions that a tumour circulation is only visible for a brief period, and with only three films it is possible to miss the whole or part of the abnormality.

An example is shown in Fig. 6 of a patient aged 47 in whom there were symptoms and signs which suggested that a hypernephroma, removed four years previously, had metastasized to the brain. A temporal deposit was seen in the routine series of three films, but when exposures were made between the normal intervals a second deposit was clearly seen in the occipital region ; this was scarcely visible in the first series and was certainly not

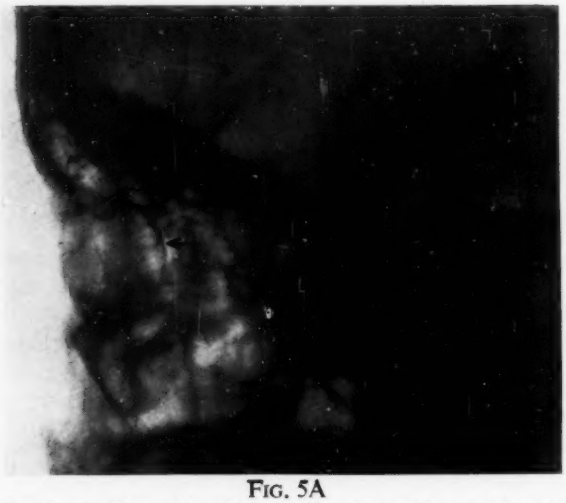

FIG. 5A

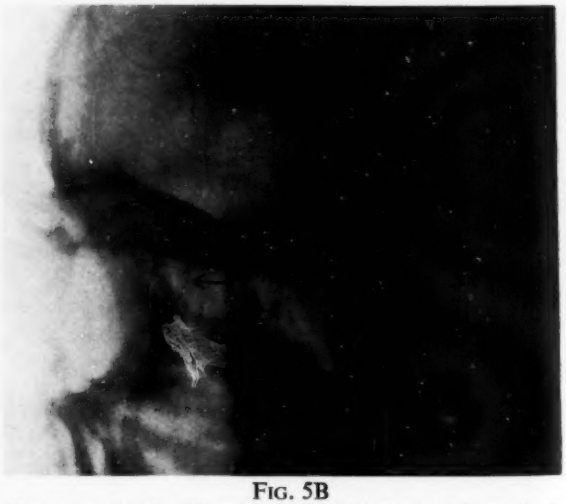

FIG. 5B

FIG. 5.—A. 5½ seconds. B. 6 seconds. Frames from serial angiograms of two cases showing filling of the choroidal plexus of the eye (←).

FIG. 6A

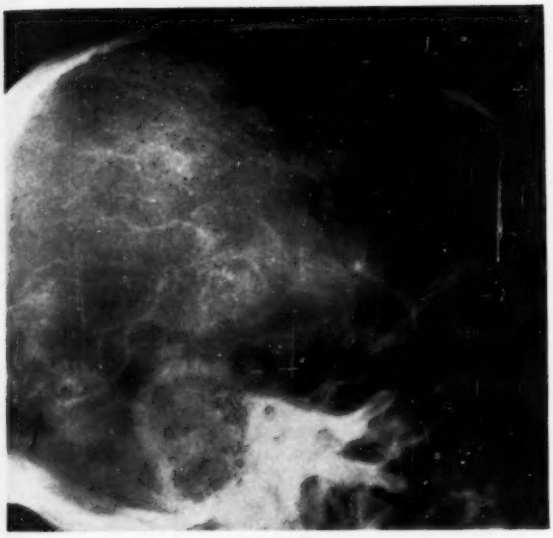

FIG. 6B

A. Arteriogram (2 seconds) from a standard series showing the tumour circulation of a metastatic hypernephroma in the temporo-parietal region (↑).

B. Arteriogram (1 second) from a series of films taken between the standard times showing another deposit in the occipital region (↑). This was not sufficiently clearly seen in any of the films of the first series for a diagnosis to be made.

sufficiently well defined for diagnosis. The presence of the second large deposit made operative removal impossible.

It sometimes happens that, when a tumour does not reveal a pathological circulation or does not lie in direct relation to any of the larger arteries, a diagnosis has to be based on the displacement of very small vessels. With the larger number of exposures obtained by the serial method there is greater opportunity of obtaining good films of these small channels (Fig. 7).

Malignant Gliomas.—The presence of arterio-venous fistulae in a tumour other than an arterio-

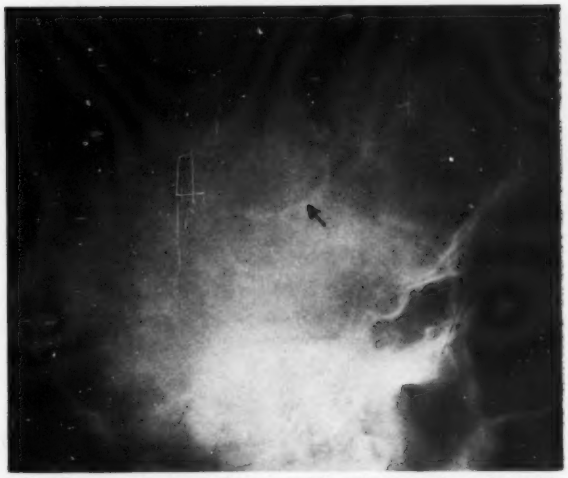

FIG. 7.—Frame at 4 seconds from a serial angiogram of a patient with a fronto-parietal glioblastoma multiforme. The localization of almost avascular tumours depends on the observation of displacements of small vessels (↑) which may fill for only a brief interval and are therefore more clearly seen in serial films. These vessels could not be identified in the previous frame (3½ seconds), and were invisible again three frames later (5½ seconds). Retouched.

venous malformation, has come to be recognized as one of the chief radiological characteristics of malignancy in a glioma. This feature is of extreme importance in the diagnosis of a glioblastoma multiforme, and with further experience it may prove that as a criterion of malignant change it is of more value than histological examination of a smear which may happen to have been taken from a part of the neoplasm in which the original non-malignant type of cell still exists.

The early filling of tumour veins can be accurately studied in serial angiograms, and the time of their

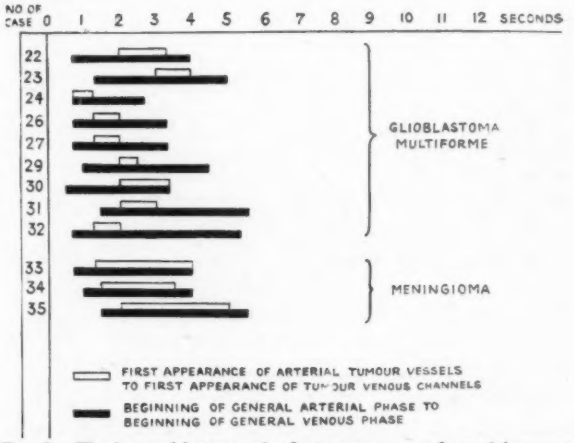

FIG. 8.—The interval between the first appearance of arterial tumour vessels and their venous efferents compared with the time between the appearance of the first arteries and the first venous channels elsewhere in the cerebral circulation. This is shown in nine cases of glioblastoma multiforme and three cases of meningioma. In two other cases of each type the tumour vessels were insufficiently clear for comparison. The rapid passage of contrast medium into the efferent vessels of the glioblastomas is clearly seen.

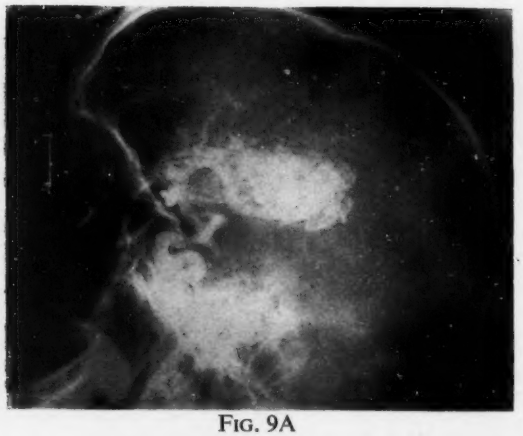

FIG. 9A

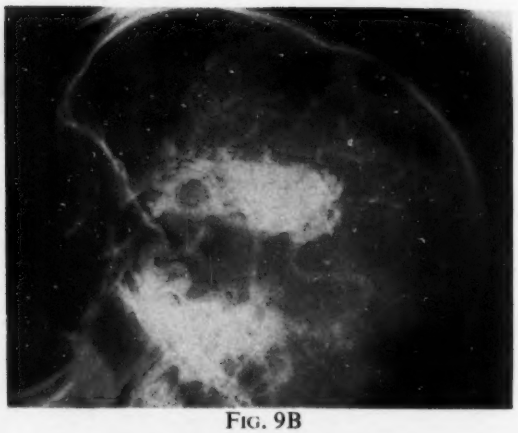

FIG. 9B

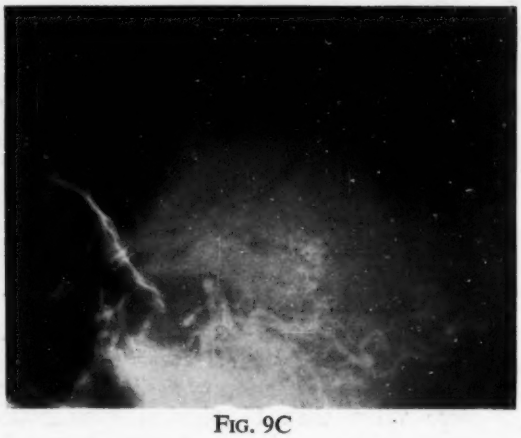

FIG. 9C

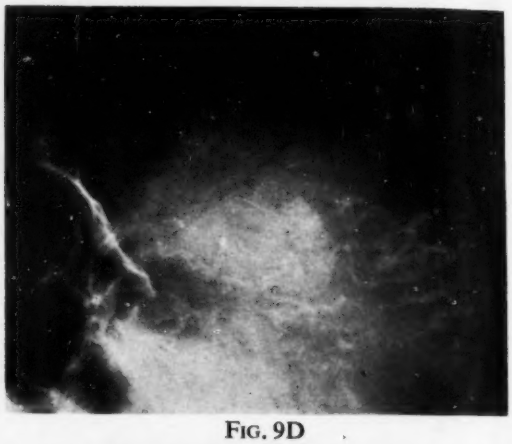

FIG. 9D

FIG. 9E

FIG. 9.—A. 1⅓ seconds. B. 2⅔ seconds.

Frames from a serial angiogram of a large arteriovenous malformation taken during an injection of the left internal carotid artery. The contrast can be seen to spread through a dense cluster of abnormal vessels, and to enter the dilated and tortuous venous efferents at an early stage. The anterior cerebral artery has not filled clearly but is just visible. The main blood flow is seen to be through the lesion.

C. 2 seconds. D. 3⅓ seconds.

Frames taken during an injection into the left vertebral artery of the same patient. The vascular abnormality is seen to be much more extensive than was first shown to be the case, different parts of the lesion being supplied by the middle and posterior cerebral arteries.

E. 6 seconds. A later film in the vertebral series shows the presence of a veil-like lake of contrast substance, lying in grossly dilated venous channels not visible after carotid injection and appearing late in the series.

appearance can be compared with that of the remainder of the cerebral venous channels. In Fig. 8 the interval between the appearance of the first arterial vessels in a tumour and the first vein leading from it is compared with the beginnings of the arterial and venous phases of the general cerebral circulation in the same case. It will be seen that the contrast passes relatively rapidly into the venous efferents of the glioblastomas, in which arteriovenous fistulae are plentiful, and with much less rapidity into those of the meningiomas. The duration of filling of tumour vessels may prove to be a valuable aid to the differential diagnosis of various types of neoplasm, but it is not possible to be definite because fistulae between arteries and veins may occasionally be found in certain meningiomas (Wickbom, 1948).

Arteriovenous Malformations.—Considerable assistance is given to the surgeon who intends to

operate on arteriovenous malformations by an accurate knowledge of the afferent and efferent vessels to such a lesion. This enables them to be occluded in the correct order, and ensures that, so far as is possible, the difficulties of the operation are foreseen.

The circulation in certain arteriovenous malformations may be extremely rapid on account of the absence of capillary resistance, and the contrast may pass so quickly through these lesions that the arteries and veins are not seen separately in films obtained at the usual interval of 2 seconds (Wickbom, 1950). Furthermore, the whole of the malformation is not always filled at the same time or from a single source. A large lesion of this type is shown in Fig. 9. The serial angiograms of this patient were performed by the internal carotid and vertebral routes, and show an extensive arteriovenous malformation supplied from each of the three large cerebral arteries, with a gradual spread of the contrast substance into different parts of the lesion. The later frames from the vertebral series (Fig. 9E) show the development of a veil-like appearance caused by venous sacs, which often fill late in the series and are not always completely outlined in any one frame. The presence of such dilated venous channels greatly increases the difficulties of operation.

The complete film obtained from a patient with an unusual type of capillary angioma was illustrated in the preliminary report (Curtis, 1949). In this there was late filling of certain abnormal vessels which would not have been apparent in the routine series of three films. This lesion has not been confirmed histologically because the patient's epilepsy is adequately controlled by medical treatment and her symptoms do not warrant surgical exploration at present.

Aneurysms.—An interesting demonstration is provided, by means of rapid serial angiography, of the duration of filling of large saccular aneurysms of the carotid siphon which may retain the contrast substance after it has left the rest of the cerebral vessels (Fig.10).

Carotico-cavernous Fistulae.—The contrast substance passes so rapidly from artery to vein in these cases that, with our present machine, the serial frames do not succeed one another quickly enough to show the stages of its passage through the fistula. We have only used the rapid serial method in one case of this nature, but in this it did not appear to provide any particular advantage over the standard technique.

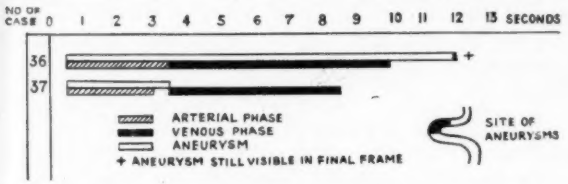

FIG. 10.—Duration of filling of two aneurysms situated on the carotid siphon. The diameter of the aneurysm in Case 36 was 2·8 cm., and that in Case 37 was 1·0 cm. Pooling of contrast occurs in the larger aneurysmal sac.

Thrombosis.—In two cases of thrombosis of the middle cerebral artery we observed a change in the extent of the territory supplied by the anterior cerebral artery (Fig. 11A), and clearly demonstrated that the ascending branches of the middle cerebral artery can in these circumstances be filled from above. In each of these cases the contrast filled the anterior cerebral artery and its named branches,

FIG. 11A

FIG. 11B

FIG. 11.—A. 3½ seconds. B. 4 seconds.

Consecutive frames from a serial angiogram of a case of middle cerebral thrombosis, showing how the contrast substance, in the absence of pressure in the reverse direction, flows through anastomotic channels into the territory normally supplied by the thrombosed vessel. Notice further filling of vessels (↑) in the second frame.

and then flowed like a fountain over the surface of the hemisphere into the areas usually supplied by the middle cerebral artery. In the films the contrast could be clearly seen to pass from the small branches of the anterior cerebral artery into the corresponding branches of the middle cerebral artery, the retrograde filling of which gradually increased in the later frames (Fig. 11B). The serial angiogram of the case illustrated was repeated at the same session after blockage of the stellate ganglion with 1% procaine. No significant change was observed, but two and a half weeks had elapsed between the onset of the clinical symptoms and the interruption of the sympathetic pathways.

These cases show that the blood supply to areas affected by thrombosis can be restored not only by recanalization of thrombosed vessels, but also by the opening up of anastomotic channels to allow the passage of blood from other main arteries. These findings are also useful in angiographic diagnosis because, when the middle cerebral vessels are poorly filled, doubt often exists as to whether this is within normal limits or due to occlusion of small branches. If retrograde filling can be demonstrated, it is clear that there is in fact a thrombosis.

Conclusions

Rapid serial angiography is of considerable value as a research technique, and, when some of the variable factors are controlled, is likely to prove as useful in studying the physiology of the circulation of the brain as it has already proved to be in the study of the circulation of other organs. A modification of the machine described was used by Daniel and Prichard (1951) in their studies of the hepatic circulation. These workers used thorotrast for their contrast medium, and for the study of physiological conditions a less irritating substance than diodone must be used; we have therefore not attempted to collect material for the study of normal physiology from among our cases. The method of serial angiography is also of considerable educational value, since knowledge of the more complete picture of the passage of contrast substance through the cerebral vessels helps in the interpretation of other angiograms.

For clinical purposes there are certain circumstances in which rapid serial angiography may provide information which is not otherwise obtainable, although for routine work the standard technique of making three exposures at 2, 4, and 8 seconds has proved adequate. The method is of greatest use in studying the circulation of arteriovenous malformations, and may give the surgeon valuable information if surgical treatment of these lesions is contemplated. The second important indication for its use is when there is difficulty in the interpretation of angiograms obtained by the standard method; for example, when the possibility of malignant change in a tumour is open to question. Lastly, the demonstration of retrograde flow, in cases in which small vessels are thrombosed, may help in the diagnosis of these lesions.

Summary

The experience obtained with rapid serial angiography since the preliminary report was made in 1949 is reviewed.

Twenty-one normal serial angiograms are discussed with reference to the sequence and duration of filling of cerebral vessels during angiography.

The appearances of the choroidal plexus of the eye in rapid serial angiograms are described.

The uses of serial angiography in the diagnosis of tumours and in depicting arteriovenous malformations are considered.

Some observations are made on the course of the blood flow in cases of thrombosis of the middle cerebral artery.

Serial angiography should be used to supplement the information supplied by the standard (three-film) technique, particularly in cases of vascular malformation and in conditions in which interpretation of the standard films is difficult. It may also be of assistance in some cases of cerebral thrombosis. The technique has great value for research and teaching purposes.

We acknowledge our indebtedness to Mr. J. B. Curtis who, with Dr. E. Schuster, O.B.E., was responsible for the development of the apparatus, and also took many of the angiograms we have reviewed. We are also grateful to Dr. D. G. Wyatt of the Nuffield Institute for Medical Research for measuring the irradiation, and to the Editor of the *British Journal of Ophthalmology* for permission to reproduce Figs. 5A and 5B.

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CHRONIC NEUROLOGICAL DISEASE AS A POSSIBLE FORM OF LEAD POISONING

BY

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It has long been known that the clinical manifestations of lesions in the nervous system produced by lead are diverse and may simulate the symptoms of various chronic neurological diseases. This suggested to early workers that lead might be an aetiological agent in such diseases.

Later, the failure to demonstrate the presence of other features of classical lead poisoning such as colic, anaemia, and basophilic stippling of the red cells in these conditions, and any correlation with exposure to an occupational hazard, demanded the modification of the original theory, and there remained the possibility that lead ingested in subtoxic amounts may eventually produce these chronic, atypical forms of poisoning.

Disseminated sclerosis is a particular example. The old theory championed by Oppenheim that lead is the causative factor was revived in a modified form by Cone, Russel, and Harwood (1934), who suggested that the demyelination is produced by lead which is mobilized from skeletal deposits before relapse. They put forward analytical results in support of this view. Lead was detected in the cerebrospinal fluid of six out of eight patients with this disease, and was estimated in the faeces and urine and also in the spinal cord of another patient. Their results for cerebrospinal fluid are not in agreement with those of Rabinowitch, Dingwall, and Mackay (1933) and Boshes (1935).

However, with the advent of more accurate and sensitive analytical methods it was realized that the findings of Cone and others were of no aetiological significance since similar amounts of lead may occur in most normal human fluids and tissue " as an inevitable consequence of life on a lead-bearing planet " (Kehoe, Thamann, and Cholak, 1933).

A new light was thrown on human demyelinating diseases by the discovery that swayback, a similar disease of lambs, was associated either with a dietary deficiency of copper or with a defect in its utilization by the nervous system, and could be prevented by the administration of copper to the pregnant ewe. Since the incidence of the disease tended to follow the geological occurrence of lead in Derbyshire and the sheep were found to have absorbed abnormal amounts of this metal from their diet, it was suggested that lead might be involved in the production of the disease (Innes and Shearer, 1940; Shearer and McDougall, 1944). This view has never been confirmed.

Campbell, Herdan, Tatlow, and Whittle (1950) reported that teeth from patients with disseminated sclerosis contained on the average a significantly higher concentration of lead than was present in the teeth of normal healthy people. They discovered a high incidence of this disease in a village where the concentration of " acetic acid soluble lead " in the garden soil was high, though the well water was not contaminated, and concluded that lead might be an aetiological factor in some cases, perhaps by antagonizing the utilization of an essential metal.

However, large skeletal deposits of lead do not necessarily indicate intoxication since they are themselves physiologically inert. The possibility that the physiological changes accompanying chronic diseases may promote the deposition of metals in the skeleton should be borne in mind. This is illustrated by the increased deposition of zinc in teeth in tuberculosis (Cruickshank, 1940).

Cases of lead myelopathy with symptoms closely similar to those of disseminated sclerosis have been described by Cone and others, by Williams (1939), and by Campbell and others. The diagnosis was based on the finding of a high concentration of lead in the fluids or tissues and the recognition of a hazard. Other points of similarity between the two conditions are the frequent increase in the concentration of cerebrospinal fluid proteins and the lowering of the platelet count (literature cited by Campbell and others).

Analogous theories of the production of acute transverse myelitis (quoted by Campbell and others) and of toxaemia of pregnancy (Letonoff, Reinhold,

Riggs, and Cohn, 1940) in certain people may be quoted, and the analysis of tissue taken at necropsy has given some support to such speculation. Hansmann and Perry (1940), from their study of the relative concentrations of lead in liver and rib, concluded that lead which has been mobilized from skeletal deposits may act as an unrecognized factor in many diseases, although it may not be possible to trace any abnormal exposure. Riggs, Letonoff, and Reinhold (1944) formed a similar opinion from their results on kidney and pituitary gland obtained from patients whose death was not adequately explained by clinical and necropsy findings. Many of them had presented neurological symptoms.

The dangers of de-leading treatment after lead poisoning have been much discussed and are relevant to this problem. Aub (1935) drew attention to the possibility that the mobilized lead may not be excreted but may circulate and be redeposited, and Kehoe (quoted by Gray, 1935) has emphasized the danger of redeposition in the nervous system.

It is apparent that this theory of the aetiology of disseminated sclerosis and other neurological conditions is only supported by circumstantial evidence, yet it has never been satisfactorily dismissed, and a direct investigation using a reliable analytical method was undertaken to fulfil an obvious need. The postulated mobilization of lead from the skeleton in toxic quantities must inevitably produce an increase in the amount of lead in circulation and this may result in an increased excretion. Accordingly the concentration of lead in the blood and cerebrospinal fluid of various patients and their urinary excretion of lead was determined. Information on the magnitude of skeletal deposits of lead in certain patients was obtained by the analysis of biopsy specimens of tibia and of teeth. The urinary excretion of coproporphyrin was also studied, since de Langen and ten Berg (1948) had shown that its elevation is an early sign of the absorption of abnormal amounts of lead, and it was argued that it should also be a sensitive indication of lead mobilization.

The estimation of lead in post-mortem specimens of tissue taken from people whose diagnosis is beyond doubt is obviously essential, yet apart from the single analysis of spinal cord recorded by Cone and others (1934) no such investigation of disseminated sclerosis has ever been reported. Values for the lead content of brain, spinal cord, liver, and bone taken from people who had undoubtedly suffered from disseminated sclerosis are presented in this paper.

Material

The subjects studied fall into four groups :—

(1) Disseminated Sclerosis.—This group includes 26 patients with disseminated sclerosis and five probable cases. The majority of these and the other neurological cases in the second group have been under observation since they were investigated and their diagnosis was recently checked personally by Dr. W. Ritchie Russell. Cases of spastic paraplegia which have not shown the characteristic relapses and remissions of disseminated sclerosis are included in the next group.

The age of these subjects at investigation ranged from 20 to 54 years, their average age being 37 years, and the duration of the disease varied from one month to 25 years (average six and a half years).

Tissue samples were obtained from five additional subjects post-mortem, and in each case the diagnosis of disseminated sclerosis was confirmed histologically by Drs. P. M. Daniel and F. D. Bosanquet.

(2) Miscellaneous Neurological.—This group contains 56 patients with other chronic neurological diseases, some of which, e.g. spastic paraplegia and peripheral neuritis, may be simulated by lead poisoning. Six children are included and the average age of the adults at investigation was 42 years. Necropsy tissue samples were obtained from two of the adults.

(3) Patients with Unusual Exposure to Lead.—Investigations were carried out on seven patients with slight non-specific symptoms, of whom six had experienced an occupational exposure to lead. The other patient (C.H.) was included in this group on the grounds that his high intake of beer (more than a gallon a day) for 38 years may have constituted an abnormal exposure which was responsible for his high lead excretion. Beer which has been contaminated by lead pipes has been known to produce poisoning when consumed in such quantities.

The analytical results obtained for these cases and the absence of haematological changes excluded the possibility of lead poisoning.

(4) Lead Poisoning.—For comparison four industrial workers who had developed lead colic through exposure to lead dust were studied. One (L.H.) had been symptom-free for two weeks when investigated. The others had blue " lead lines " on the gums and all had anaemia and basophilic stippling of the red cells. No signs of nervous involvement could be detected.

Intramuscular injections of B.A.L. were given to a few patients in groups (1) and (2) as a therapeutic trial measure and to provide a possible means of

assessing the deposits of lead in soft tissue by observing its effect on urinary lead excretion.

Analytical Methods

Determination of Lead.—An absorptiometric "dithizone" micro-method which is more sensitive, convenient and selective than most previous methods was developed for these investigations and will be published in detail elsewhere (Butler and Irving, 1952).

Its sensitivity is such that an analysis can be performed on 20 ml. of urine, 5 ml. of blood, 5–10 ml. of cerebrospinal fluid, 400 mg. of dried soft tissue or 100 mg. of dried bone after "wet" ashing.

The utilization of the reversion technique introduced by Irving, Andrew, and Risdon (1948, 1949), besides eliminating several of the impractical requirements of most published methods, viz. a standard solution of this notoriously unstable reagent and a rigid control of the *p*H of extraction and the concentration of other coloured species present, enables an efficient separation of lead from up to ten times as much bismuth to be achieved.

The possibility of interference from bismuth is of considerable importance in investigations of this nature. While the traces of this metal which are present in most normal human fluids and tissues may not be sufficient to lead to significant errors if they are not removed, the presence of bismuth cannot be safely ignored when dealing with tissue samples, particularly bone, from hospital patients, since it is the basis of many pharmaceutical preparations such as may be prescribed for disseminated sclerosis.

The precautions taken to minimize contamination by adventitious traces of lead followed current practice, and blanks in the region of 0·2 μg. were consistently obtained.

All the glass apparatus was of Pyrex, and was specially cleaned before use with caustic soda solution and concentrated nitric acid (boiling where possible) and then rinsed thoroughly with tap, distilled, and lead-free, glass-distilled water. Stainless steel needles used for the collection of blood were cleaned by boiling with dilute acetic acid and rinsing with water as described above.

Concentrated acids, ammonia, and carbon tetrachloride (A.R. grade) were redistilled in all Pyrex apparatus, and salts (A.R. grade) were purified by extracting their aqueous solutions with a carbon tetrachloride solution of dithizone.

Collection of Specimens.—Urine was collected over 24 hours rather than over shorter periods, since Webster (1941) and Kehoe (1947) have shown that there is a marked diurnal variation in urinary lead excretion. It was passed into a Pyrex 2- or 3-l. bottle with the aid of a funnel where necessary. Any precipitates were dissolved by the addition of hydrochloric acid before samples were taken for analysis.

Blood was collected by venipuncture in an ungreased Pyrex syringe and then expelled into a Pyrex tube provided with a stopper and containing a little solid ammonium citrate as an anticoagulant. Cerebrospinal fluid was taken by lumbar puncture with a stainless steel needle and collected in a Pyrex tube after discarding the first few drops.

Large samples of soft tissue were taken at necropsy in the normal way and afterwards uncontaminated specimens were removed from the interior of these samples with specially cleaned instruments and placed in metal-free Pyrex dishes. Pyrex glass instruments were used for E.D., W.W., T.A., and M.B. while those employed for taking the other specimens were made of stainless steel.

Discs of tibial cortex weighing 1–2 g. were removed with a trephine and placed in metal-free Pyrex tubes. The teeth analysed were all unfilled, and, since the distribution of lead in teeth is unknown, only whole, non-carious specimens were collected. They were put into metal-free Pyrex tubes immediately after extraction and washed with hot, metal-free water.

All tissue was dried by vacuum desiccation and heating at 110°C.

Estimation of Coproporphyrin in Urine.—The method was essentially that of Schwartz, Hawkinson, Cohen, and Watson (1947). The coproporphyrin in a 100-ml. sample of urine (less for patients with lead poisoning) was extracted with an ether-acetic acid mixture and after separation from other porphyrins was estimated fluorimetrically using a Pulfrich photometer under ultra-violet light and safranin as a standard (Jope and O'Brien, unpublished).

Results and Discussion

The results obtained are given for individual subjects in Tables I–IV and VI, and in Tables V and VII are collectively compared with the normal ranges established by other workers who used less refined methods of comparable accuracy for estimating lead.

The neurological cases (groups 1 and 2) will now be considered in relation to the possibility of lead poisoning or an abnormal absorption or mobilization of lead. The severe disability of some of these patients limited the number of specimens which could be studied.

There was in no case either a history of colic or vomiting or evidence of anaemia or abnormal basophilic stippling of the red cells. An unusual exposure to lead could be traced for only two patients, F.F. and F.R., and both had disseminated sclerosis. The former had been a painter but his urinary excretion of lead (50 μg./24 hrs.) was similar to that of other patients (Table I). F.R. had been exposed to lead dust in a car factory for three months just before the onset of symptoms. The concentration of lead in a sample of cerebral white matter obtained at necropsy nine years later was not abnormally high (Table VI).

Urinary Excretion of Lead.—The excretion of more than 100 μg. of lead in 24 hours is taken as

TABLE I

VALUES FOR LEAD CONCENTRATION IN BLOOD AND C.S.F. OF PATIENTS WITH DISSEMINATED SCLEROSIS AND FOR URINARY EXCRETION OF LEAD AND COPROPORPHYRIN

Case	24-hr. Urinary Excretion			Blood (μg. Pb/100 ml.)	C.S.F. (μg. Pb/100 ml.)
	Vol. (ml.)	Pb (μg.)	Copro-porphyrin (μg.)		
H.S.†	820	5	—	—	<4
,,	730	46*	—	—	—
E.C.	1,300	47	—	—	—
,,	1,080	97*	—	—	—
L.S.	1,460	12	—	—	—
,,	2,060	25*	—	—	—
W.H.	1,530	35	—	—	—
,,	2,130	43	—	—	—
F.F.	1,280	50	—	—	—
E.P.	1,590	9	—	11	—
V.B.	2,700	97	—	—	20
,,	2,640	—	53	—	—
J.L.†	1,010	43	—	20	2·5
R.M.	1,350	8	25	7	2
,,	1,320	28	103	—	—
,,	1,090	18	183	—	—
,,	1,730	—	190	—	—
A.B.	1,710	5	142	6·5	<1
,,	2,200	—	105	—	—
M.L.	1,080	31	4	19	—
,,	1,810	48	6	—	—
A.R.	1,105	25·5	31·5	10·5	—
D.M.	690	19	32	8	—
K.P.	935	25	28	6·5	—
R.A.†	2,650	73	—	—	—
P.A.	1,080	—	108	2	<1
B.A.	1,880	—	60	8	5·5
I.S.	1,590	—	66	—	—
H.W.	490	—	53	—	—
S.L.†	410	—	36	—	—
D.B.	1,700	—	48	—	7
M.M.	2,150	—	43	—	—
M.K.†	—	—	—	35	—
W.S.	—	—	—	15	4
C.B.	—	—	—	27	—
W.W.	—	—	—	—	7
B.B.	—	—	—	—	12
M.R.	—	—	—	—	27
S.M.	—	—	—	—	2
D.F.	—	—	—	—	2
M.H.	—	—	—	—	12

Suspected cases indicated by †. * denotes that B.A.L. was injected during the collection of the specimen.

TABLE II

VALUES FOR LEAD CONCENTRATION IN BLOOD AND C.S.F. OF PATIENTS WITH VARIOUS NEUROLOGICAL DISEASES AND FOR URINARY EXCRETION OF LEAD AND COPROPORPHYRIN

Case	Diagnosis	24-hr. Urinary Excretion			Blood (μg.Pb/100 ml.)	C.S.F. (μg. Pb/100 ml.)
		Volume (ml.)	Pb (μg.)	Copro-porphyrin (μg.)		
W.L.	Spastic paraplegia	1,770	64	—	—	—
		1,220	195*	—	—	—
L.B.	Spastic paraplegia	1,390	12	—	—	—
		2,000	41*	—	—	—
E.S.	Spastic paraplegia	1,770	25	—	—	—
		1,970	82*	—	—	—
R.A.	Familial paraplegia	1,100	5	16	—	—
		1,110	16*	26	—	—
O.N.	Post-vaccinal encephalopathy	1,335	52	—	21	6
H.F.	Spinal cord disease	1,820	38	53	13·5	—
M.R.	Ascending myelitis	260	—	9	—	—
M.C.	Myelopathy ? cause	950	—	18	—	—
L.T.	Cerebellar ataxia	—	—	—	—	26
A.D.	Friedreich's ataxia	—	—	—	3	—
B.S.	Friedreich's ataxia	—	—	—	—	2
C.W. (Age 7)	Schilder's disease	600	13	—	—	—
		800	26*	—	—	—
		1,100	10	—	—	—
D.E. (Age 4)	? Schilder's disease	—	—	—	—	<2
C.B.	Peripheral neuritis	1,180	23	—	—	—
		990	46*	—	—	—
N.W.	? Peripheral neuritis	2,010	36	—	—	—
		1,440	126*	—	—	—
J.D.	Peripheral neuritis	1,750	5	—	—	5
L.R.	Peripheral neuritis	1,470	30	7	—	—
T.T.	Peripheral neuritis	1,510	10	—	—	—
H.W.	Peripheral neuritis	2,270	88	—	—	23
M.W.	Peripheral neuritis	1,620	—	97	—	—
T.E.	Chronic neuritis with paralysis	—	—	—	13	—
T.W.	Shoulder girdle neuritis	1,740	62	—	16	32
W.M.	Local neuritis	2,690	5	—	—	2

[Continued on next page

TABLE II—*continued*

Case	Diagnosis	24-hr. Urinary Excretion			Blood (μg. Pb/100 ml.)	C.S.F. (μg. Pb/100 ml.)
		Volume (ml.)	Pb (μg.)	Copro-porphyrin (μg.)		
E.H.	? local neuritis	2,860	50	63	20	—
J.W.	Primary sensory neuropathy	—	—	—	—	9
W.C.	Acute infective polyneuritis	—	—	—	—	8
N.W.	Motor neuron disease	1,120	67	—	—	—
R.S.	Motor neuron disease	720	12	—	—	8
W.G.	Motor neuron disease	1,470	—	125	—	—
V.G.	Motor neuron disease	—	—	—	20	10
F.A.	Motor neuron disease	—	—	—	12	2
J.P.	Motor neuron disease	—	—	—	21	2
W.H.	Motor neuron disease	—	—	—	—	2
K.L.	Motor neuron disease	—	—	—	—	9
A.B-C.	? Motor neuronitis + arthritis	—	—	—	31	4·5
M.K.	Peroneal muscular atrophy	1,370 870	41 74*	— —	— —	— —
A.T.	Muscular dystrophy	2,115	89	—	22	4
A.I.	Muscular dystrophy	—	—	—	28	4
A.T.	Muscular dystrophy	—	—	—	27	—
W.G.	Muscle wasting ? cause	—	—	—	—	6·5
S.W.	Wilson's disease	1,290 1,605 1,120 1,960 1,490	18 12 25 25 5	98 46 12 20 12·5	10 11 17 — —	— — — — —
C.B.	Wilson's disease	—	—	—	6	—
G.D.	? Wilson's disease	3,765	52	64	11	—
W.T.	Congenital athetosis	940 2,180 1,950	— 25 53*	134 100 125	— — —	— — —
G.G.	Choreo-athetosis	1,490 1.070	24 34*	98 14	— —	— —
H.M.	Parkinson's disease	1,690 1,270	17 54*	— —	— —	— —
M.R. (Age 13)	Charcot-Marie disease	1,280	55	21	19·5	—

TABLE II—*continued*

Case	Diagnosis	24-hr. Urinary Excretion			Blood (μg. Pb/100 ml.)	C.S.F. (μg. Pb/100 ml.)
		Volume (ml.)	Pb (μg.)	Copro-porphyrin (μg.)		
R.G.	Myasthenia gravis	1,060	5	—	—	—
E.J.	? Syringo-myelia	—	—	—	—	2
G.F.	Prolapsed lumbar disc	—	—	—	—	14
J.W.	Cerebral tumour	1,065	7	—	—	2
A.S. (Age 6/12)	Cerebral tumour	—	—	—	—	2
R.B. (Age 6)	Encephalitis	1,320	50	—	—	9
J.S.	Convulsions	—	—	—	—	13

* indicates that B.A.L. was injected during the collection of the specimen.

evidence of abnormal absorption resulting from unusual exposure. It may also indicate the mobilization of tissue deposits providing the mobilized lead is excreted.

No definite level above this limit can be associated with the onset or disappearance of symptoms of lead poisoning, and the excretion of 100–200 μg. of lead may occur in the absence of symptoms and haematological changes. This is illustrated by the values for the excretion of B.B. and C.H. (Table III) and the patients with lead colic (Table IV).

Past workers have shown that an abnormal urinary lead excretion is the first sign of abnormal absorption, occurring before an elevation in coproporphyrin excretion (Johnson and Whitman, 1950) and blood lead concentration (Kehoe, Thamann, and Cholak, 1935). The results for B.B., a solderer, are in agreement with these findings. After poisoning the elimination of the excess lead from the tissues is gradual. J.L. (Table IV) had an abnormal lead excretion (160 μg./24 hrs.) over three months after his blood film had become normal. The determination of urinary lead excretion is thus a very sensitive test of abnormal absorption and probably of mobilization.

It is apparent from Table V that the excretion of all the neurological patients was within the normal limits. The average excretions for the two groups were almost identical (33 and 32 μg.Pb/24 hrs. respectively) and were less than the output of all the patients with abnormal exposure (Table III).

These figures, therefore, provide no evidence of an abnormal absorption of lead, of a mobilization of it, or of a past attack of lead poisoning in any

subject with chronic neurological disease. The majority of the patients with disseminated sclerosis were investigated when showing active symptoms, and in three cases (V.B., J.L., R.M.) the duration of the disease was less than three months. The second group includes a boy, (C.W.) aged 7, with Schilder's disease, which is pathologically very similar to swayback in lambs. Verhaart (1941) described a similar case with high concentrations of lead in the brain and liver, but could not identify a hazard. It is interesting to note also that the high urinary copper excretion in Wilson's disease is not accompanied by an abnormal lead excretion. Subsequent work (unpublished) has shown that the zinc output is also normal in this disease.

The administration of B.A.L. to 14 neurological patients (three with disseminated sclerosis) produced a significant increase in the 24-hourly excretion of lead (usually twofold-fourfold) in each case (Tables I and II). Four intramuscular injections of 100 mg. of B.A.L. in propylene glycol were given at three-hourly intervals, the first at the beginning of the 24-hour period. The amount by which the urinary lead excretion was increased (an abnormal excretion was produced in only two instances) does not indicate the presence of large amounts of lead in soft tissue.

This mobilization of lead, which may have been accompanied by an increased excretion of the essential metals copper and zinc (unpublished work), produced no clinical change. It may be mentioned that Furmanski (1948) claimed that smaller doses of B.A.L. had a beneficial effect on patients with severe peripheral neuropathy, but was reluctant to consider this to be due to the removal of some intoxicating heavy metal.

Lead in Blood.—Lead has been found in the blood of normal unexposed subjects in concentrations up to 89 μg./100 ml. (Table V), and, according to Cantarow and Trumper (1944), the majority have concentrations below 60 μg./100 ml. As with urinary lead excretion there is no definite threshold value at which symptoms of poisoning appear in exposed people. The patients with lead colic had concentrations of 85 to 96 μg./100 ml. when showing symptoms, and after clinical remission the two patients investigated showed values of 65 and 62 μg./100 ml. (Table IV). Six weeks afterwards when their blood films were normal these levels had fallen to 44–56 μg./100 ml. Two subjects with unusual exposure showed values within this range (Table III).

The highest concentration found in a neurological patient (Tables I and II) was 35 μg./100 ml. The

TABLE III

VALUES FOR LEAD CONCENTRATION IN BLOOD OF MISCELLANEOUS PATIENTS WITH UNUSUAL EXPOSURE TO LEAD AND FOR URINARY EXCRETION OF LEAD AND COPROPORPHYRIN

Case	Occupation	Symptoms	24-hr. Urinary Excretion			Blood (μg. Pb/100 ml.)
			Vol. (ml.)	Pb (μg.)	Copro-porphy-rin (μg.)	
H.L.	Paint sprayer (16 years)	Paraesthesia of legs	2,980	45	40	12·5
B.C.	Painter	Paraesthesia of left leg, vomiting	1,375	—	110	—
B.B.	Solderer (5 years)	Muscular weakness in arms	1,235	116	30	51
P.A.	Painter	Colic	1,310	42	—	—
J.R.	Paint sprayer (1 year)	Colic	1,200	72	72	—
G.S.	Painter (37 years)	Abdominal pains, muscular rigidity	2,045	81	245	—
C.H.	Butcher (heavy beer drinker for 38 years)	Muscular weakness in legs and fingers	1,730	125	110	41

TABLE IV

VALUES FOR LEAD CONCENTRATION IN BLOOD AND C.S.F. OF PATIENTS WITH LEAD COLIC AND FOR URINARY EXCRETION OF LEAD AND COPROPORPHYRIN

Case	24-hr. Urinary Excretion			Blood (μg. Pb/100 ml.)	C.S.F. (μg. Pb/100 ml.)
	Vol. (ml.)	Pb (μg.)	Copro-porphy-rin (μg.)		
J.Q.	765	165	4,600	92	17
	860	255	3,700	—	—
	955	250	2,600	—	—
	2,120	204	4,100	65	—
	2,020	111	1,300	—	—
	Interval of five weeks				
No symptoms, Blood film normal	1,630	160	1,960	—	—
	1,420	85	1,240	56	—
	1,890	147	1,960	—	—
J.L.	1,175	350	4,200	96	24
	2,065	540	1,300	—	—
	1,320	400	3,200	—	—
	1,880	193	4,900	62	—
	1,640	196	1,000	—	—
	Interval of five weeks				
No symptoms, Blood film normal	1,470	123	850	44	—
	1,400	110	870	—	—
	1,480	183	680	—	—
	1,470	185	1,060	48	—
	1,900	190	610	—	—
	Interval of seven weeks				
	3,290	160	353	—	—
J.I.	1,360	115	—	85	—
L.H. No symptoms	1,950	190	—	38	—

TABLE V

COMPARISON OF VALUES FOR LEAD CONCENTRATION IN BLOOD AND C.S.F. AND FOR URINARY EXCRETION OF LEAD AND COPROPORPHYRIN WITH NORMAL RANGES

Author	Subjects	24-hr. Urinary Excretion		Blood (μg.Pb/100 ml.)	C.S.F. (μg.Pb/100 ml.)
		μg.Pb.	μg. Copro-porphyrin		
Cantarow and Trumper (1944) and authors since 1933 cited	Normals	0–100	—	0–80	—
Watson and Larson (1947) and authors cited	Normals	—	0–120	—	—
Letonoff and others (1940)	Normals	—	—	9–50	—
Chalmers (1940)	Normals	—	—	36–89	—
Brown (1946)	Normals	—	—	11–81	—
Schmitt and Basse (1937)	Normals	—	—	—	15–38
Cantarow and Trumper (1944)	Patients with no neurological symptoms	—	—	—	1–40
Butler (this paper)	Patients with D.S. (Table I)	5–97 (33)	4–190 (69·5)	2–35 (13·5)	<1–27 (ᔕ7)
,, ...	Miscellaneous neurological patients (Table II)	5–89 (32)	7–134 (55)	3–31 (17)	<2–32 (ᔕ8)
,, ...	Patients with exposure (Table III)	42–125	30–245	12·5–51	—
,, ...	Patients with lead colic (Table IV)	115–540	1,300–4,600	85–96	17 and 24
,, ...	Patients with normal blood film after Pb colic (Table IV)	85–190	353–1,960	44–56	—

(The figures given in brackets are average values)

TABLE VI

VALUES FOR LEAD CONCENTRATION (P.P.M. DRY WEIGHT) IN TISSUES OF PATIENTS WITH NEUROLOGICAL DISEASE

Case	Age	Diagnosis	Duration of Disease (yrs.)	Cerebral White Matter	Spinal Cord	Liver	Tibial Cortex	Teeth		
								Incisor	Premolar	Molar
A.B.	31	D.S.	4	—	—	—	7·0*	—	—	—
W.W.	32	D.S.	3	—	—	5·0	—	—	—	—
D.F.	35	D.S.	3	—	—	—	12·0*	—	—	—
P.A.	36	D.S.	14	—	—	—	8·3*	—	—	—
B.A.	37	D.S.	2/12	—	—	—	7·0*	—	—	—
M.A.	43	D.S.	10/12	—	—	—	—	30·0* 35·1*	28·8* —	13·0* 19·7*
E.D.	56	D.S.	10	0·76	1·59	4·83	37·9	—	—	—
F.R.	58	D.S.	9	1·1 0·7†	—	—	—	—	—	—
T.A.	59	D.S.	7½	0·54	—	3·39	22·5	—	—	—
M.B.	64	D.S.	—	<1	1·0	<1	15·0	—	—	—
N.W.	29	Motor neuron disease	5	—	—	—	16·0*	—	—	—
J.P.	42	Motor neuron disease	8/12	—	—	—	10·5*	—	—	—
F.A.	50	Motor neuron disease	7/12	—	—	—	35*	—	—	—
R.S.	65	Motor neuron disease	1	<1	0·17	2·9	—	—	41·2	—
R.K.	2½	? Schilder's disease	1 8/12	—	—	—	3·2*	—	—	—
K.A.	38	Convulsions. Cerebral cortical atrophy	7/12	0·35	1·25	2·95	—	—	—	—

Additional results : W.W., Rib 9·5. M.B., Kidney 0·8.

* Specimens obtained by biopsy.
† This result is for a specimen containing a plaque of demyelination.

TABLE VII

COMPARISON OF VALUES FOR LEAD CONCENTRATION IN TISSUES (P.P.M. DRY WEIGHT) WITH THOSE OF OTHER WORKERS

Author	Diagnosis	Brain	Liver	Kidney	Tibia	Teeth	Rib
Hansmann and Perry (1940) and authors cited	Various (no exposure to Pb or mobilization)	0–1·99	0–43·74	1·0–110·05	20·4–289·5	0·15–274·7	0–86·42
Riggs and others (1944) ..	Other neurological disease	—	—	3·6–11·4	—	—	—
Campbell and others (1950) ..	Normals (age 40–50)	—	—	—	—	25·7–95·1	—
,, ..	D.S. (age 40–50)	—	—	—	—	27·0–123·7	—
,, ..	Normals (age 60–70)	—	—	—	—	74·5–90·3	—
,, ..	D.S. (age 60–70)	—	—	—	—	129·3	—
Butler (this paper)	D.S.	0·54–1·1	<1–5	0·8	7·0–37·9	13·0–35·1 (age 43)	9·5
,, ..	Other neurological disease	0·35 and <1	2·9 and 2·95	—	3·2–35	41·2 (age 64)	—

TABLE VIII

LEAD CONTENT OF BLOOD AND TISSUE OF NEUROLOGICAL PATIENTS

Blood or Tissue	Group (1)	Group (2)
Whole blood	0·02–0·33*	0·03–0·29*
Cerebral white matter ..	0·08–0·17	0·05 and <·15
Spinal cord	0·15 and 0·24	0·03 and 0·19
Liver	<0·2–1·0	0·58 and 0·59
Kidney	0·16	–
Tibial cortex	2·33–12·63	1·07–11·67
Teeth	11·72–31·62	37·12
Rib	3·17	–

*Expressed as p.p.m. fresh weight.

average for the two groups was almost the same, viz. 13·5 and 17 μg./100 ml. (Table V). These figures thus provide no evidence of abnormal absorption or mobilization.

Urinary Excretion of Coproporphyrin.—Normal healthy adults may excrete up to 120 μg. of coproporphyrin in their urine in 24 hours. This coproporphyrin consists of a mixture of the Types I and III isomers in which the former predominates (Schwartz, Hawkinson, Cohen, and Watson, 1947). It has been established that in lead poisoning a great increase in the excretion of coproporphyrin III occurs, due probably to a disturbance in the synthesis of haemoglobin.

Waldman and Seideman (1950) and Maloof (1950) have recently confirmed the observation of de Langen and ten Berg that with exposure to lead the urinary coproporphyrin excretion becomes abnormal long before haematological changes and symptoms appear.

The coproporphyrin excretion of two of the patients with lead colic was determined and was much more abnormal than their lead excretion (Table IV). It remained high when the haematological changes disappeared, and over three months afterwards J.L. had an excretion of 353 μg./24 hours. The estimation of urinary coproporphyrin excretion is thus a sensitive test of a past attack of lead poisoning as well as of an abnormal absorption of lead.

However, this change is non-specific, and smaller elevations have been observed in poisoning by other chemicals, anaemias, infectious disease, including the common cold (Jope and O'Brien, unpublished data), and following the administration of drugs, e.g. sulphonamides and salicylates. Therefore this abnormality, like stippling, cannot be taken as a diagnostic sign of lead poisoning until abnormal amounts of lead have been demonstrated in the blood and urine.

Two patients with disseminated sclerosis (R.M. and A.B., Table I) and one with peripheral neuritis and one with congenital athetosis (W.A. and W.T., Table II) showed slightly abnormal excretions of coproporphyrin. Three consecutive specimens of urine were collected from R.M. and these contained 25, 103, and 183 μg. of coproporphyrin respectively. A course of histamine injections was started during the collection of the last specimen and may have been responsible for the abnormal excretion which was again observed (190 μg.) five months later. It was not associated with a raised lead excretion. A.B. had been given a mixture of metallic salts, including those of cobalt, copper, chromium, manganese, beryllium, daily by mouth for several weeks, eight months before the specimens were collected.

The abnormal excretion of W.A. and W.T. could not be correlated with any pathological condition or therapy. The normal excretion of the patient with Wilson's disease (S.W.) may indicate that this is not a condition of copper poisoning.

It is concluded that lead had not entered the blood stream in sufficient amounts to cause an increased coproporphyrin excretion in patients with disseminated sclerosis and the other neurological diseases studied.

Lead in Cerebrospinal Fluid.—The low sensitivity of older analytical methods has enabled comparatively little work to be done on the normal concentration of lead in the cerebrospinal fluid. However, the significance of the concentration of lead in this fluid in the diagnosis of lead encephalopathy is doubtful, since it appears to bear no definite relation to the symptoms (Hay, 1950) and high values may be found in lead poisoning with no neurological manifestations (Cantarow and Trumper 1944).

The concentrations found in the two groups of neurological patients (Tables I and II) were not significantly different and were all lower than the normal limit of 40 μg./100 ml. suggested by past work. This value was also not exceeded in lead colic although the concentration in the blood was abnormal, a finding which has been reported in similar cases many times in the literature. A child with lead encephalopathy studied subsequently showed a cerebrospinal fluid lead concentration of 7 μg./100 ml. concurrently with a blood concentration of 170 μg./100 ml.

Lead in Tissues.—The results examined above do not exclude the remote possibility that in disseminated sclerosis and certain other neurological diseases lead may be intermittently released from skeletal deposits and transported to the central nervous system so quickly that the rise in blood lead concentration is merely transient and is not reflected in an increased lead and coproporphyrin excretion. An alternative theory is that the central nervous system develops an abnormal affinity for lead and retains toxic amounts from normal blood concentrations, any mobilization from bone being relatively unimportant. Clearly a final answer to this question can only be supplied by the analysis of brain and spinal cord.

The values obtained for the concentration of lead in the cerebral white matter (frontal lobe), spinal cord, and other tissues of subjects in Groups I and II are given in Table VI and are not significantly different for the two groups. Further, it is apparent from Table VII that they all lie well below the upper limits of the results recorded by previous workers for various people with no abnormal exposure to or mobilization of lead. This table does not include the results of Hijman (1935) which are considerably higher than those of all other workers. Campbell and others (1950) do not state whether their results are for dry or fresh weight.

It is of some interest to note that the lead content of five teeth from M.A., a case of disseminated sclerosis, show a dependence upon the type of tooth (Table VI). The values for tibial cortex show no regular variation with age or the duration of the disease.

In Table VIII the concentration limits for lead in the blood and tissues of the two groups of subjects expressed in p.p.m. fresh weight, are compared. In calculating these values it was assumed that the specific gravity of blood was 1·06 and the water content (w/w) of the tissues was as follows :— brain and spinal cord, 85%; other soft tissue, 80%; bone, 66%; and teeth, 10% (Hansmann and Perry).

It is obvious that there had been no significant accumulation of lead in the cerebral white matter and spinal cord. It had been retained to some extent by the liver and deposited in much larger concentrations in the skeleton, particularly in the teeth, as is normal. The values obtained for these concentrations are not consistent with the finding of Campbell and others of abnormal deposits of lead in teeth in disseminated sclerosis.

Thus the analysis of tissue taken at necropsy has shown that in at least four cases lead had not been directly responsible for the production of the lesions of disseminated sclerosis and provided no evidence of any abnormality in the distribution of lead between the skeleton and soft tissue in this disease. Copper and zinc have also been estimated in these specimens, and these results will be presented in a separate communication together with a description of the cases and the post-mortem findings.

Summary

With an improved analytical method it was found that patients with disseminated sclerosis showed no significant difference from those with other chronic neurological diseases as regards their urinary excretion of lead and its concentration in the blood, cerebrospinal fluid, and tibial cortex, which in all cases was within the normal limits.

Patients with confirmed lead poisoning were studied for comparison and showed that an abnormally high urinary excretion of lead and coproporphyrin is maintained long after clinical remission and the disappearance of haematological changes. The coproporphyrin excretion of the two groups of neurological patients was not significantly different and with a few exceptions was within the normal range.

The injection of neurological patients with B.A.L. consistently produced an increase in urinary lead

excretion (usually two- to fourfold). This response in terms of increased lead excretion bore no apparent relation to the diseases studied, nor did its magnitude indicate the presence of abnormal amounts of lead in circulation and soft tissue.

The lead content of necropsy samples of tissue, including brain and spinal cord, obtained from subjects whose diagnosis of disseminated sclerosis was confirmed histologically showed that lead was not responsible for the lesions in these people and that there had been no mobilization of lead from the skeleton.

It is concluded that the studies reported do not support the view that lead plays a part in the aetiology of disseminated sclerosis and certain other chronic diseases of the nervous system.

This research was suggested by Dr. W. Ritchie Russell and I am grateful to him and his staff for their cooperation and advice. My thanks are also due to Mr. J. R. P. O'Brien for many helpful suggestions and stimulating discussions; to Messrs. B. Cooke and G. Newman for invaluable technical assistance; to Mrs. S. Harrold for carrying out some of the coproporphyrin estimations; to Drs. P. M. Daniel and F. D. Bosanquet for necropsy material; and to Dr. D. McAlpine (the Middlesex Hospital) for collecting teeth. I am indebted to the Medical Research Council for a personal grant and also a grant for technical assistance.

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THE ACTION OF DECAMETHONIUM IODIDE (C.10) IN MYASTHENIA GRAVIS

BY

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Myasthenia gravis is a chronic disease characterized by abnormal fatigue of the voluntary muscles. This fatigue is due to a progressive failure of conduction at the myoneural junction after muscle contraction, and can be temporarily relieved by prostigmine sulphate (Walker, 1934). The exact nature of the neuromuscular block remains obscure, and an analysis of neuromuscular transmission in myasthenia gravis and, in particular, of the quantitative changes in motor end-plate response to acetylcholine are fundamental to the understanding of the disease.

Decamethonium iodide can be considered to have an acetylcholine-like effect on skeletal muscle but differs in not being hydrolysed in the tissues (Paton and Zaimis, 1950).

The Mode of Action of Decamethonium Iodide (C.10)

In 1949 Paton and Zaimis investigated the action of the polymethylene bistrimethylammonium salts and found that the muscular relaxation was maximal in the methonium series when 10 carbon atoms were present in the aliphatic linking chain. Investigation of the decamethonium salts showed that their site of action differed from all the other known muscle relaxants. Fundamentally, these salts act in a way analogous to acetylcholine ; that is, they produce depolarization of the muscle surface membrane in the region of the motor end-plate, and a contraction of the muscle fibres. In the case of decamethonium iodide, however, the muscle fibre remains in a depolarized state for a prolonged period, when it is unable to respond to nerve impulses—a condition of neuromuscular block.

Doses of up to 3 mg. were given intravenously to 16 normal conscious volunteers (13 male and three female) and resulted in the development of muscular weakness. The first symptoms in all subjects were visual and occurred in 20 to 30 seconds after the injection. They consisted of strabismus with diplopia and marked ptosis with a feeling of " heavy eyelids ". In the majority of cases the diplopia was vertical. The initial symptoms passed off rapidly so that vision had almost returned to normal in five minutes. Inconstantly, a feeling of tightness, particularly in the jaw and calf muscles, was experienced. The second phase of symptoms consisted of muscle weakness starting two to four minutes after the first injection. The neck, trunk, and limb muscles were affected, and, if doses of 3·0 to 3·5 mg. were used, a partial loss of voice and a weakening of the swallowing reflex occurred. With such dosages respiration was mildly embarrassed. It was observed that the action of decamethonium iodide was more prolonged in the resting than in the exercised limb.

Paton and Zaimis (1950) have pointed out that in the assessment of the action of decamethonium salts in conscious subjects the potentiating effect of adrenaline must be considered. In our series of normal and myasthenic subjects the same technique has been used on both, and we have no reason to suppose that adrenaline secretion, which increases the stimulant action of decamethonium and changes the pattern of muscle response, has influenced the results of one group more than the other.

Technique

To measure the effect on muscle power of decamethonium iodide the ulnar nerve was stimulated percutaneously at the elbow or wrist with supramaximal stimuli delivered at a rate of 10 per second, and muscle action potentials were recorded by skin electrodes from the hypothenar muscles.

The patient was placed on a couch in a position of rest and the 0·3 millisecond stimulus was delivered from an earth-free source. The skin electrodes were placed so as to give an integrated action potential which was used as an index of the number of muscle fibres responding. To detect errors due to any change in position of the skin electrodes, the action potentials were observed both during the paralysing and the recovery phase ; the final action potential after recovery was matched with the initial one. The potentials after amplification

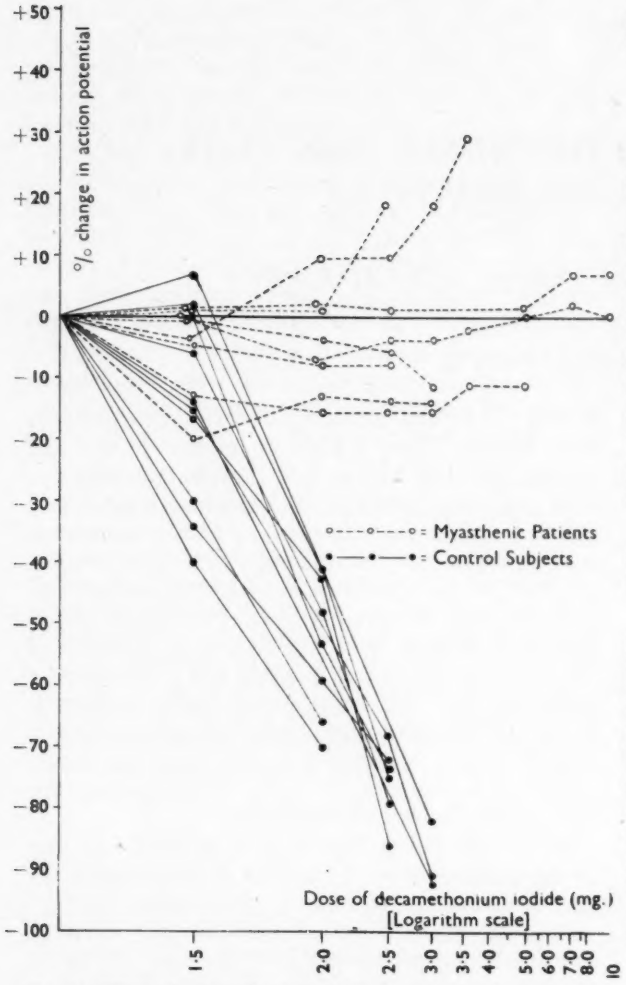

FIG. 1.—Effect of decamethonium iodide on muscle action potential in normal controls and myasthenic subjects.

(time constant of the amplifier, 30 milliseconds) were photographed from a cathode ray oscillograph, the time base of which was triggered by the stimulator. The film was exposed for five seconds every two minutes, allowing 50 stimuli and responses to be recorded on one frame and thus a constant potential wave form was ensured. Peak-to-peak measurements were used as an index of the number of contracting muscle fibres and the results expressed as a percentage change of the initial action potential. No alteration in nerve conduction time or in the duration of the muscle action potential was observed during the experiment.

All drugs were withdrawn from the patient 24 hours before investigation. Each case of myasthenia gravis was fully investigated and the diagnosis confirmed. In these investigations electromyography was used to assess the degree of muscle fatigue and the response to neostigmine. Decamethonium iodide was given into an arm vein in divided doses: an initial dose of 1·5 mg., followed in four minutes by 0·5 mg.: 0·5 mg. was then given at two-minute intervals until a drop of the muscle action potential or clinical muscle weakness occurred.

Results

Table I shows the effect of intravenous decamethonium iodide on the muscle action potential in 16 controls.

In all patients except one a dose of 2·0 mg. resulted in a significant reduction in amplitude of the recorded action potential. In the exception a dose of 2·5 mg. produced a significant reduction. The change in the action potential could not be related to the dose per unit of body weight. It will also be seen that in normal subjects doses of 3·0 to 3·5 mg. decamethonium iodide partially paralyse the vocal cords and also abolish the swallowing reflex. In these doses some degree of respiratory embarrassment occurs.

Table II shows the response of 11 cases of myasthenia gravis to intravenous decamethonium iodide.

All except one case showed tolerance in the peripheral muscle examined by the electromyograph. The dosage, however, was in nearly all cases limited by the onset of weakness in the bulbar muscles before the full extent of the peripheral tolerance could be determined. It is of great interest that one case, J.G., was given 10 mg. on two separate occasions before and after thymectomy without any effect. In this series seven cases were investigated before and four after thymectomy. The one patient with myasthenia whose peripheral muscles did not show a tolerance to decamethonium iodide was investigated only after thymectomy.

Case Histories

Case 3.—Miss J. G., aged 20, was admitted to St. Thomas's Hospital in December, 1950, with a history of drooping of both eyelids for four months. Eighteen months previously she had visited her doctor complaining of diplopia, which cleared up. Prostigmine did not appear to have any marked effect on her symptoms although she was improved by ephedrine and relapsed when this was withdrawn. No abnormal fatigue of the peripheral muscles was observed at any time or demonstrated electromyographically. She was given decamethonium iodide on three occasions and was able to tolerate 10 mg. without showing any signs of weakness. It is remarkable that she was able to walk normally after this very large dose of the drug. No change in the muscle action potential was observed with 10 mg. Thymectomy was carried out in January, 1951, and a thymus weighing 28·5 g. was removed. Since that time she has had no attacks of ptosis or other muscle weakness. She was again given 10 mg. of decamethonium iodide in June, 1951, and again it was without effect either clinically or electromyographically.

TABLE I
CONTROL PATIENTS

No.	Case	Weight (kg.)	Change (%) in Electromyographic Response after Graded Doses of Decamethonium Iodide											Other Effects				
			1·5 mg.	2·0 mg.	2·5 mg.	3·0 mg.	3·5 mg.	5·0 mg.	6·0 mg.	7·0 mg.	8·0 mg.	9·0 mg.	10·0 mg.	Diplopia	Ptosis	Muscle Spasms	Dysphagia Aphonia	Respiratory Embarrassment
1	S.C.	88	−34	−59	−72	—	—	—	—	—	—	—	—	+	+	—	—	—
2	D.B.	66·7	−40	−70	—	—	—	—	—	—	—	—	—	+	+	+	—	—
3	B.L.	65	−30	−66	—	—	—	—	—	—	—	—	—	+	+	—	+	—
4	I.C.	66·2	−14	—	−68	−90	—	—	—	—	—	—	—	+	+	+	+	—
5	E.T.	69	−6	−48	−82	—	—	—	—	—	—	—	—	+	+	—	—	—
6	E.J.	68	−8	−10	−46	—	—	—	—	—	—	—	—	+	+	—	—	—
7	C.M.	77	+50	+20	−64	—	—	—	—	—	—	—	—	+	+	+	—	—
8	A.R.	70·7	+2	−42	−75	—	—	—	—	—	—	—	—	+	+	+	—	—
9	D.M.	55	−16	−40	−86	—	—	—	—	—	—	—	—	+	+	—	+	—
10	F.M.	64	0	−52	−74	—	—	—	—	—	—	—	—	+	+	+	+	—
11	H.D.	70	+10	—	—	−82	—	—	—	—	—	—	—	—	+	—	+	+
12	R.B.	78	−14	—	—	−92	—	—	—	—	—	—	—	—	+	—	+	+
13	J.R.	58·5	—	−82	—	—	—	—	—	—	—	—	—	+	+	—	+	—
14	L.T.	—	—	—	−76	—	—	—	—	—	—	—	—	+	+	—	—	—
15	P.J.	55·3	—	—	—	—	−94	—	—	—	—	—	—	—	—	—	—	+
16	E.F.	46·7	−50	−56	−64	—	—	—	—	—	—	—	—	+	+	+	—	—

TABLE II
MYASTHENIC PATIENTS

No.	Case	Weight (kg.)	Change (%) in Electromyographic Response after Graded Doses of Decamethonium Iodide											Other Effects				
			1·5 mg.	2·0 mg.	2·5 mg.	3·0 mg.	3·5 mg.	5·0 mg.	6·0 mg.	7·0 mg.	8·0 mg.	9·0 mg.	10·0 mg.	Diplopia	Ptosis	Muscle Spasms	Dysphagia Aphonia	Respiratory Embarrassment
1	B.L.	72·6	0	0	+20	—	—	—	—	—	—	—	—	—	+	—	+	—
2	E.H.	65·3	−4	—	—	—	—	—	—	—	—	—	—	—	—	—	+	—
3	J.G. (i)	52·6	−4	−8	−8	—	—	—	—	—	—	—	—	—	—	—	—	—
	(ii)	52·6	0	−4	−6	−6	−6	−12	—	—	—	—	—	—	—	—	—	—
	(iii)	52·6	0	−8	−4	−4	−2	0	−4	+2	+3	+5	0	—	—	—	—	—
	(iv)	52·6	0	0	0	0	0	0	+6	+6	+8	+8	+8	—	—	—	—	—
4	C.D.	50·8	−10	—	—	—	—	—	—	—	—	—	—	—	—	—	+	—
5	M.G.	—	−20	−12	−13	−14	—	—	—	—	—	—	—	—	—	—	+	—
6	L.M.	56·7	−4	+10	+10	+20	+30	—	—	—	—	—	—	—	—	—	+	+
7	B.S.	63·5	+20	+28	—	—	—	—	—	—	—	—	—	—	—	—	+	—
8	R.D.	70·7	−32	−40	−32	−28	−36	−40	—	—	—	—	—	—	—	—	—	—
9	F.H.	69·8	−16	−16	−16	−16	−12	−12	—	—	—	—	—	—	—	—	+	—
10	A.C.	64·4	−10	−16	—	—	—	—	—	—	—	—	—	—	—	—	+	—
11	F.P.	57·1	−83	—	—	—	—	—	—	—	—	—	—	+	—	—	—	—

Case 8.—Mr. R. D., aged 30, attended the Out-Patient Department in February, 1951, complaining of drooping of both eyelids for one year. In 1945 he had been under investigation for diplopia and at that time weakness of the left inferior oblique muscle was discovered. On clinical examination in February, 1951, he was found also to have abnormal fatigue of the left tibialis anterior and deltoid. An electromyogram of the left tibialis anterior also showed excessive fatigue. Thymectomy was carried out in April, 1951, and a thymus weighing 23 g. was removed. To date (August, 1951) his condition has not improved. He was given decamethonium iodide in June, 1951, and was able to tolerate 5 mg. without any change in the muscle action potential. At this stage, however, the ptosis was worse and he complained of weakness of the legs, worse in the left leg.

It is noteworthy that when weakness occurs in myasthenia gravis after the administration of decamethonium iodide its onset is first in those muscles already rendered weak by the disease. These are generally the bulbar muscles, which appear in myasthenia subjects to be more sensitive than other muscles to decamethonium. This selective action is well illustrated by the onset of weakness in the case of R.D., first in the left leg and then later in the normal right leg.

Case 6.—Mr. L. M., aged 41, was first seen in the hospital in November, 1950, with a history of weakness in the arms and legs, ptosis, and dysphagia. At the time of his admission he was taking 35 mg. of prostigmine sulphate three times a day, but in spite of this dosage suffered from marked weakness and fatigue, being almost bedridden. Thymectomy was carried out in November, 1949, and a small thymus was removed. His post-operative course was stormy, and respiration was so severely embarrassed that he had to be placed in a Drinker's apparatus for six days. He states that since operation, although he continues to take 30 mg. of prostigmine sulphate five times a day, he is now able to do a normal day's work. Electromyographic fatigue tests before and after thymectomy showed excessive fatigue and no apparent change. Decamethonium iodide was administered in June, 1951, and a total of 3·5 mg. was given, which, although producing no change in the action potential of the right hypothenar muscles, produced marked weakness of those muscles in which myasthenic fatigue was greatest. This became so severe that a paralysis of swallowing and respiration occurred.

Discussion

Lanari (1937) and Harvey and Lilienthal (1941) concluded from their experimental work that the muscles of myasthenic patients were hypersensitive to acetylcholine. The latter workers, following Lanari's method, used intra-arterial injections of 20 to 40 mg. of acetylcholine into the brachial artery. In myasthenic patients the injection produced a violent contraction of the muscles supplied by the artery, whereas normal subjects experienced only a transitory paralysis (Harvey, Lilienthal, and Talbot, 1941). Wilson and Stoner (1947) completely failed to demonstrate any striking difference between the response of the muscles of myasthenic and normal subjects to acetylcholine. They commented, however, that loss of power, which might be attributed to a depressant level of acetylcholine, was seen more often in normal subjects than in patients with myasthenia gravis. In a more recent contribution Wilson, Maw, and Geoghegan (1951) have failed to find any evidence of increased cholinesterase activity in this condition.

Our results indicate a generalized tolerance of the muscle fibres of myasthenic patients to decamethonium iodide, particularly marked in those patients in whom the only clinical evidence of myasthenia is ptosis and diplopia. However, when the muscle fatigue is more widespread the tolerance is more difficult to demonstrate. For, although it is still marked in the unaffected muscles, it is reduced in those muscles affected by the disease. This resistance to the depolarizing action of decamethonium iodide may be due either to the destruction of the compound before it is able to act on the muscle fibres, or to an inherent resistance of the end-plate of myasthenic muscle fibres to its action.

It is known that with both acetylcholine and decamethonium compounds a stimulatory phase (contraction) precedes the period of muscle paralysis. With decamethonium iodide the stimulatory phase is periodically seen as fascicular twitchings and muscle spasms in the jaw and calf muscles of both myasthenic and normal subjects. With acetylcholine, on the other hand, as this substance is rapidly destroyed, a situation can theoretically arise wherein a blood concentration adequate to bring about depolarization is only momentarily achieved. Thus stimulation of the muscle fibres will occur and the stage of paralysis, which normally follows the stimulatory phase, is so short that it is no longer clinically evident. Similarly, a dose which will produce paralysis in normal muscles may only lead to stimulation in less sensitive muscles, as we believe myasthenic muscle to be. It would therefore appear possible that Harvey and Lilienthal, using 20 to 40 mg. of acetylcholine, may have produced a paresis in their normal patients whereas this dosage was only sufficient to produce a stimulatory action in the tolerant muscles of myasthenic patients. Such an interpretation of their work would be compatible with our results and at the same time would be in agreement with the views

expressed by Wilson and Stoner. Direct evidence of the tolerance of the muscles of myasthenia subjects to acetylcholine is supplied by Buchtal and Engbaek (1948) who found that with small doses (0·2–0·3 mg.) of acetylcholine intra-arterially, normal patients showed a motor response (stimulatory phase) whereas myasthenic patients appeared to be tolerant in that no response occurred unless far greater doses were given. Acheson (1944) also found that the muscles of myasthenic patients were a little less sensitive to acetylcholine than those of normal subjects, but stated that the difference was not great on a small number of observations.

Summary

The effect of intravenous decamethonium iodide on the muscles of 16 normal, control subjects and 11 cases of myasthenia gravis is described. The finding that patients with myasthenia gravis appear to possess a tolerance to this compound is discussed.

We wish to thank Dr. J. St. C. Elkington, Physician-in-Charge of the Neurological Department, and Mr. N. R. Barrett, Surgeon to St. Thomas's Hospital, for permission to investigate cases under their care. It is also a pleasure to acknowledge the help of Dr. Bauwens, Physician-in-Charge, Physical Medicine Department, St. Thomas's Hospital. Miss Jean Davenport rendered valuable secretarial assistance.

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CASE REPORT: REFLEX EPILEPSY AND PERIPHERAL INJURY

BY

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In discussing the significance of reflex epilepsy Critchley (1933) stated that an incoming stimulus would hardly provoke convulsive phenomena unless there was a state of supercharge in the central nervous system. Holmes (1927) described cases in which a cortical lesion apparently caused the disturbed peripheral response to a specific stimulus, and he considered that the appropriate external stimulus may excite epileptic symptoms if the corresponding part of the cortex is in an unstable state. A number of the cases in Critchley's series were associated with severe structural changes in the brain, and he also quotes a case of Rosenhain's in which attacks were precipitated by irritating the stump of an amputated finger, a necropsy eventually showing a tumour of the parietal lobe of the opposite hemisphere. Dawson (1947) has since shown experimentally that a peripheral stimulus can produce an electrical response over the contralateral cortex.

The association between the epileptic response and peripheral injury in some cases of reflex epilepsy has been reviewed recently by Parsons-Smith (1948) who added a case of his own. This was the case of a man who had cerebral cysticercosis and subsequently sustained a peripheral nerve injury, after which focal and generalized fits were precipitated by the passage of a stimulus through the injured peripheral nerve.

The following case also shows evidence of abnormal cortical function and peripheral nerve injury but differs from Parsons–Smith's case in that the patient suffered from traumatic epilepsy for many years before he sustained the peripheral injury which led to the development of reflex fits.

Case Report

The patient was a widower, aged 62, who came of healthy stock, and from whom no family history of epilepsy or other nervous disorder could be obtained. He was in good health until 1917 when he sustained a penetrating wound of the right frontal region while on active service in France. The right orbit was also injured and this resulted in a permanent squint and almost complete loss of vision in the right eye. He made a satisfactory recovery from the immediate effects of the wound but about 12 months later he began to suffer from fits. These were typical major epileptic convulsions and at first occurred three or four times a week. The attacks gradually became less frequent and in recent years have occurred at intervals of about six months. They have always been preceded by an aura of slight giddiness. In 1927, i.e. 10 years after the head injury, he injured his left foot. He was rather vague about the details of this injury, but it evidently resulted in swelling and ulceration over the dorsum of the foot and took a long time to heal. After this he became aware that his fits were sometimes related to the peripheral injury, in that painful stimulation of the left foot might precipitate an attack.

He remained in good general health and had been free from attacks for six months, when, on March 5, 1949, he fell and again injured the left foot and ankle. He was taken to hospital and found to have marked swelling and ecchymosis over both malleoli, especially on the lateral side where there was acute tenderness. A radiograph showed a simple fracture of the lower third of the left fibula. A plaster cast was applied and he was allowed to return home. He attended the fracture clinic a week later when it was decided to renew the plaster. The old cast was being cut with plaster shears when he had a fit. The attack began with clonic movements of the left foot and leg, spreading to the left arm and face, and followed rapidly by a generalized convulsion and loss of consciousness. When he was examined about 10 minutes later, he had recovered consciousness but was still confused and unable to give a history. A brief neurological examination was now carried out, and while the left plantar response was being tested he had another fit. After making a further attempt to examine him, it was realized that the stimulus applied to the outer border of the sole of the left foot in eliciting the plantar response was precipitating the fits. Several further attacks were produced in rapid succession by this means. He was then admitted to hospital for a few days until the pain and swelling of the ankle had subsided, when he was discharged home in a walking plaster. No further fits occurred in hospital but he was now taking ½ gr. phenobarbitone three times a day. Further progress at the fracture clinic was uneventful and the plaster was eventually removed without incident.

He was re-examined as an out-patient after an interval of seven months when a detailed neurological examination was made. He was a heavily built, elderly man

who walked with a slight limp. There was a depressed scar over the right frontal region extending slightly upwards and laterally from the medial third of the supra-orbital ridge to a point two inches above the pinna. An underlying bony defect could be felt. There was a marked external squint and only hand movements could be detected with the right eye. The visual acuity of the left eye was 6/12 (uncorrected). There was marked atrophy of the right optic disc and gross pallor of the surrounding retina. Numerous areas of deep pigmentation at the sites of old haemorrhages were also seen. The left fundus appeared normal. The scar, and the skin over the greater part of the distribution of the first division of the right fifth nerve, were anaesthetic to pin-prick. Both corneal reflexes were brisk and sensation was normal over the remainder of the face and head. The other cranial nerves were normal. There was no weakness of the upper or lower limbs or trunk. Coordination was normal. The deep reflexes of the upper limbs were brisk and equal on both sides. The left knee and ankle jerks were slightly more active than those on the right and the lower left abdominal reflex was absent. Both plantar responses were flexor. Appreciation of all forms of sensation on the left side of the body was slightly impaired except over the lateral aspect of the lower third of the left leg and the outer border of the left foot, where there was marked hyperaesthesia. The hyperaesthetic area corresponded to the skin distribution of the sural nerve. There was a circular, depressed scar, ¾ in. in diameter, on the medial side of the left foot, and an irregular scar, 2½ in. × 1 in., over the lateral aspect of the dorsum of the foot. Both scars were anaesthetic.

There were no abnormal physical signs in the cardiovascular, respiratory, or digestive systems. The blood pressure was 160/100. The urine contained no abnormality.

A radiograph of the skull was reported on as follows:—

> " A bony defect is shown at the right frontal region, presumably due to an old injury. A dense opacity is shown in the mid-line just above the floor of the anterior fossa and anterior to the anterior clinoid processes. ? Metallic foreign body from old injury. There appears to be some reaction round it."

He had had three fits since his discharge from hospital seven months before, each attack having been precipitated by excitement. An attack occurred soon after he arrived at the hospital for re-examination. He was in an excited state on arrival and was very apprehensive about the unusual interest which was being taken in his case, and these emotional factors probably precipitated the fit. This attack began with clonic movements of the left foot, as in the previous attacks, but consciousness was not lost and he recovered completely within two minutes. The neurological examination was then carried out without incident until the left plantar response was tested. The firm stroking stimulus applied to the outer border of the sole of the foot at once precipitated a typical Jacksonian fit which began in the part stimulated. The attack was confined to the left side of the body and consciousness was not lost. Further identical attacks were readily produced by the same stimulus and by the application of a painful stimulus (pin-prick) but light touch and a tickling stimulus had no effect. Neither was there any response to thermal stimulation. The trigger zone was confined to the hyperaesthetic area on the outer margin of the foot. Stimulation of the remainder of the sole was without effect, and there was likewise no response to stimulation of the area of hyperaesthesia on the lateral aspect of the lower third of the leg.

The result differed from that seen seven months earlier in that the attacks were now localized to the left side, they were brief, and consciousness was not lost. The patient had taken no drugs for several months so that it would appear that the cortex was either in a less irritable state, or that the threshold to the appropriate peripheral stimulus had increased.

Discussion

This case confirms the view of Holmes that peripheral stimulation may excite an epileptic response if the corresponding part of the cerebral cortex is in an irritable state. In discussing the mechanism of reflex epilepsy, the writer of an annotation in the *Lancet* (1948) states that a study of all the effective stimuli makes it clear that in most instances there is an abnormality in the pathway responsible for the afferent impulse. This abnormality may be in the receptor organ, in the peripheral nerve or spinal cord, or, more often, in the central receiving area in the cerebral hemispheres. Parsons-Smith (1948) considers that in those cases associated with peripheral injury there may be some abnormality in the reflex arc on the afferent side between the periphery and the cortex. The evidence of the present case supports this view.

In Parsons-Smith's case the actual nerve injury did not serve as a noxious stimulus to the reflex, but it seemed that the stimulus of light touch was altered as the result of the injury and served to detonate a focal cortical outburst when applied to the area supplied by the injured nerve. In the case described above, the patient had been subject to traumatic epilepsy for 10 years before he sustained a peripheral nerve injury. The actual injury did not precipitate an epileptic attack, but he became aware that subsequent fits were sometimes related to painful stimulation of the site of the injury. When the same limb was injured again after a further interval of 12 years, a painful stimulus to the injured part precipitated a generalized convulsion. This occurred within a week of the injury, when the foot and ankle were still swollen and painful. Further generalized fits were readily produced by the application of a painful or pressure stimulus to the foot. Seven months later it was still possible to produce focal fits by applying the appropriate

stimulus to an area of hyperaesthesia corresponding to part of the distribution of the injured peripheral nerve. The history that, following the first injury to the foot, fits were sometimes precipitated by painful local stimulation, together with the presence of hyperaesthesia, suggests that the threshold to pain was lowered in the area supplied by the injured peripheral nerve, and that this was sufficient to cause a focal discharge from the corresponding area of cortex which was already in an unstable state, when the appropriate stimulus was applied. The second peripheral injury probably resulted in a further lowering of the threshold, with a corresponding increase in the ease with which the fits could be precipitated. When the patient had made a complete recovery from the second injury stimulation of the hyperaesthetic area precipitated focal fits, without loss of consciousness. As no drugs had been taken for several months, the reduction in the severity of the reflex fits was probably due to recovery from the second injury with consequent raising of the threshold to painful stimulation to its previous level. This case differs from Parsons-Smith's and from those described by Holmes in that a painful or deep pressure stimulus was the specific trigger, whereas they found that a light tickling touch was effective, and the sensations of pressure and pain did not act as excitants. In one of Critchley's early cases, however, focal fits were precipitated by scratching the sole of the foot when testing the reflexes, as in the present case.

Summary

A case of traumatic epilepsy is described, in which focal and generalized fits were precipitated by applying a specific sensory stimulus to the site of a peripheral nerve injury.

This case confirms the view that peripheral stimulation may excite an epileptic response if the corresponding part of the cerebral cortex is in an unstable state.

The probable effect of peripheral injury on the threshold to local sensory stimulation is discussed.

I wish to thank Dr. L. W. Smith for permission to report this case; Dr. Macdonald Critchley for his criticism; and Miss D. D. Hayes for her help in tracing the patient.

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BOOK REVIEWS

The Educability of Cerebral Palsied Children. By M. I. Dunsdon. (Pp. 164. 21*s.*) London : George Newnes. 1952.

"The main purpose of the present research was to study . . . cerebral palsied children, in order that facts rather than assumptions and impressions only, should provide a sound basis . . . for their educational care." This statement from the introductory chapter to this little book is very adequately followed up in the subsequent text. The author's approach is balanced and critical. The term "cerebral palsy" is taken to include spastics, athetotics, mixtures of these two, and certain cases showing ataxias, tremors, and rigidities due to cerebral disease of the newborn. The number of these cases—an estimate, based on returns from local authorities in England and Wales, is about 5,300—is large enough to call for special attention, quite apart from the problems presented by their aetiology, and the correlation of their signs and symptoms with the locality of brain damage. Chapters are devoted to the assessment of educability both by the measurement of I.Q. with various orthodox tests, and by examining other factors such as verbal ability, appreciation of spatial concepts, and specific sensory deficits. These chapters contain much useful, interesting, and largely new information. The application of Bender's "visual Gestalt maturation test", for instance, confirms the marked upsets in spatial appreciation and judgement that have often been deduced from the behaviour of these children. A surprisingly high incidence of some degree of hearing loss also emerges from this study. Apart from motor, sensory, and intellectual ability, however, the author emphasizes also the importance of factors such as emotional stability and powers of perseverance in deciding the educability of a given case. The immediate practical importance of such findings for the planning of their education hardly needs emphasizing. What is perhaps of greater importance to the neurologist in the long run is that the facts Miss Dunsdon has assembled about these disabilities may ultimately be correlated with the site and extent of brain lesion in individual cases : and the result will be an increase in our knowledge of how the brain—both cortex and basal ganglia—works. The book is likely to be of considerable value to all those who have to deal with cerebral palsy.

Die Hirngeschwülste in biologischer und morphologischer Darstellung. By K. J. Zülch. (Pp. 232 ; 83 figures. DM. 24.60.) Leipzig : Johann Ambrosius Barth. 1951.

This monograph is important, as it is based on over 3,000 cases investigated by the author in the Department of Tumour Research of the Max Plank Institute, Bochum-Langendreer, which is under the direction of Professor Toennis. The approach to the problem is comprehensive and includes, apart from macroscopic and histological descriptions of tumours, chapters on historical aspects, aetiology, classification, frequency, age incidence, and so forth. Although some of the results are a restatement of facts known from previous surveys, and others, especially in the statistical sections, require consolidation (as the author himself emphasizes) there remains much that should be of interest to the English neurologist working in this field. A welcome feature is a comprehensive and up-to-date list of references to the German and—rare in recent German contributions—to the non-German literature. The strict economy in paper, printing, and illustrations somewhat reduces the instructive value of the book.

Modern Headache Therapy. By Arnold P. Friedman. (Pp. 164. 28*s.*) London : Henry Kimpton. 1951.

Recent work has thrown some light on the physiology of headaches occurring without serious physical disease, and Wolff ("Headache and Other Head Pain." By H. G. Wolff. O.U.P. 1948. New York) has contributed more than anyone to this. As a result of these discoveries special headache clinics have begun to appear, and this book is the result of the author's experience at one of them in New York. It is primarily intended for the general practitioner who has to deal most frequently with sufferers from headache, and is short and readable. On first introduction one receives some surprises, such as the statement that trigeminal neuralgia is most often within the distribution of the first or third division, and the implication that a medulloblastoma may be missed if the size of the blind spot is not charted as a routine. But further acquaintance reveals a comprehensive and comprehensible outline of various types of headache, their diagnosis and treatment, and the chapter on migraine is especially worth reading for the many practical details it includes.

Introduction to Clinical Neurology. By Gordon Holmes. Second edition. (Pp. 189 ; illustrated. 12*s.* 6*d.*) Edinburgh : E. & S. Livingstone. 1952.

This book first appeared in 1946, and has now been brought up to date in a second edition. It is not a textbook, but, as its title indicates, it describes the information that may be elicited from the history and clinical examination. It provides in writing the instruction which those who have been at Sir Gordon Holmes's ward rounds and lectures have received by word of mouth, and many will be grateful for the opportunity of enjoying what was formerly available only to relatively few. No major changes have been found necessary, but the section on the hypothalamus has been enlarged in view of its increasing clinical importance, and that on the motor system has been amplified.

A Synopsis of Neurology. By W. F. Tissington Tatlow, J. A. Ardis, and J. A. R. Bickford. (Pp. 523; 84 figures. 30*s*.) Bristol: John Wright. 1952.

This book makes no pretence to be more than its title indicates, a synopsis for reference and quick revision, and within this limit it is successful and should be popular with those revising for examinations. Two of the three authors of this synopsis of neurology are psychiatrists, and it may be that it has been written to meet the needs of candidates for the Diploma in Psychological Medicine.

Textbook of Clinical Neurology. By J. M. Nielsen. Third edition. (Pp. 709; 212 figures. 75*s*.) London: Cassell & Co. Ltd. 1952.

This is a large and beautifully produced book of some 700 pages, now in its third edition. Although it contains a great deal of information, including some that has only recently been established, it is in many ways a disappointing work. There is a tendency to present syndromes and disease entities as lists of isolated findings strung together and often attached to some convenient eponym. This is to some extent compensated for by excellent diagrams and sections illustrating the site of lesion; but somehow the guiding thread of integrative action in the nervous system, which is so continuously illustrated in clinical practice and makes neurology both a practical art and a fascinating intellectual exercise, seems missing. In discussing clinical cerebral localization Dr. Nielsen relies more than many neurologists would be prepared to do on explanations based on anatomical "centres" and connecting fibres rather than on circuits which consider parts of the brain, perhaps widely separated spatially, as each playing an essential part in function. His view tends to give, especially to mental phenomena, a mechanical interpretation based on "neurograms" and "engrams" which continually breaks down in clinical practice. Sections on treatment, so often a neglected part of neurology, are up to date, and it will be of interest to English neurologists to see that intravenous procaine and sympathetic block are now put forward as routine treatment for early cerebral thrombosis, though perhaps the exhibition of wine or whisky, also advocated, will be a more popular therapy! No mention is made, however, of anticoagulants, now widely tried in selected cases. The use of B.A.L. in polyneuritis of obscure aetiology (Guillain-Barre syndrome) is advocated, but reports so far hardly justify a very strong advocacy.

The paper, printing, and binding of this book are luxurious, but the price will ensure it the fate of other luxury goods these days.

A Textbook of Clinical Neurology. By I. S. Wechsler. Seventh edition. (Pp. 801; illustrated. 47*s*. 6*d*.) London: W. B. Saunders. 1952.

This is the seventh edition of a textbook which was first published in 1927. It has therefore continuing support from the medical and particularly the student public. It will continue to be popular because the author has managed to consider all the essentials of neurology, and to explore some of its by-ways in under 800 pages of text. The general layout is anatomical. This has disadvantages, as diseases closely linked aetiologically, e.g., Charcot-Marie-Tooth and Déjerine-Sottas disease or Friedreich's ataxia and the cerebellar degenerations, have often to be treated in separated sections. On the whole the book covers the subject fairly fully, but there is little critical appraisal of views on aetiology or treatment—for instance the statement (without further explanation) that trigeminal pain is a rare symptom of frontal tumours, might be confusing to the student—and recent information is sometimes lacking. Thus the section on poliomyelitis is certainly out of date; and though Landry's paralysis is recognized as a manifestation rather than a disease entity, no mention is made of porphyria in this connexion. Several chapters still seem perforce to be devoted to neurosis in most neurological textbooks: but the treatment can hardly be anything but inadequate, and the tradition would now be more honoured in the breach. Also the familiar pictures of "motor points" (after Erb) would not be greatly mourned if they faded from the neurological landscape; and this book, in common with many others, might well take note of the information on segmental sensory representation revealed by more modern neurological and neurosurgical work. Also if prints of cerebral angiograms are now to become a routine in textbooks, it would be as well to establish at once the tradition of giving some diagram of the normal for comparison. On the credit side, however, must be mentioned some excellent coloured reproductions of the fundus oculi, and 33 pages on the history of neurology, clearly a labour of love and a most welcome addition to the book.

The Diagnosis of Nervous Diseases. By the late J. Purves-Stewart and C. Worster-Drought. Tenth edition. (Pp. 962; 388 figures. 50*s*.) London: Edward Arnold & Co. 1952.

The tenth edition of this book is published under the joint authorship of the late Sir James Purves-Stewart and Dr. Worster-Drought, his colleague at the West End Hospital for Nervous Diseases, London. As its title implies, it is concerned largely with the examination of the nervous system, discussed in conjunction with clinical descriptions of the relevant diseases, a method which adds to its value for the student and practitioner. There is a tendency for most neurological texts to aim at completeness by including both a résumé of all neuroanatomy and physiology and some mention of all adjuvant diagnostic tests. The present book follows this trend. It may be doubted, however, whether this is still desirable now that these subjects often each require a large volume for adequate treatment. Brief mention of them with references to fuller treatment would allow more room for clinical description and still give opportunities for interesting and variegated material, often most useful and memorable for those attempting neurological diagnosis.

The purely clinical parts of this work are well done, though the illustrations are of uneven merit. The book

will no doubt continue to be useful " as a clinical guide to senior students ", but now that it is approaching its fiftieth year of publication, it will soon require more radical revision.

Textbook of Psychiatry. By Eugen Bleuler. Translated by A. A. Brill, with a biographical sketch by Jacob Shatzky. (Pp. 635 ; illustrated. $7.50.) New York : Dover Publications, Inc. 1951.

This re-issue of Bleuler's " Textbook of Psychiatry " has coincided with the English translation of his classical work on schizophrenia. Thus we have in the two volumes an easily accessible statement of his views.

His evolution of the " group " schizophrenia out of the " entity " dementia praecox has assured him of an enduring place in the annals of psychiatry. Apart from this, he was essentially Kraepelinian in outlook, with much of Kraepelin's descriptive rigidity. Notwithstanding Dr. Shatsky's foreword to this volume, Bleuler was no Freudian, and indeed he paid only lip service to the holistic and dynamic approach implicit in psychoanalytical doctrine. Moreover, it is doubtful whether, in the light of our increasing knowledge of the affective possibilities underlying the most bizarre reactions, we are justified today in retaining within the compass of the schizophrenic group many heterogeneous and undifferentiated reactions.

Nevertheless, this book remains a masterly presentation by a great clinician, although its appeal to the modern psychiatrist will be more in its value as a historical document than in its use as a practical textbook. Indeed, he may find it salutary to peruse it, if, all too conscious of puzzlement as to where psychiatry is going, he looks backwards and sees how far it has come in so short a time.

The book is well produced, but the illustrations, which have naturally dated, are rather terrifying, and there will be few regrets that an era, the essence of which they seem to reflect, is rapidly passing.

Frontal Lobotomy and Affective Behaviour. By J. F. Fulton. (Pp. 159 ; 20 figures. 21*s*.) London : Chapman & Hall. 1952.

This book comprises the Salmon memorial lectures for 1951. Although the affective changes associated with frontal lobotomy are reviewed, it has a considerably wider scope than its title might imply. In 1937 Papez suggested a neuronal substrate for emotion, at that time purely speculative, and added as an apologia " emotion is such an important function that its mechanism, whatever it is, should be placed on a structural basis ". It is with the evidence for such neuronal mechanisms that this book is concerned. Having reviewed briefly the history of neurological enquiry into emotional expression, the author goes on to discuss the modern evidence for autonomic representation in hypothalamus, thalamus, and fore-brain ; and for the view that the hippocampus and structures closely connected with it, such as the cingulate gyrus, the orbital surface of the frontal lobe, and the anterior temporal cortex, are concerned with elaboration of emotion, and particularly with the interplay of emotional and intellectual reactions. Details of functional localization within the cortical areas concerned are to some extent still an incomplete jig-saw puzzle, but a good many pieces seem fairly firmly in place ; thus, sham rage, abnormal placidity, hyperactivity, and generalized vasodilatation have well-defined sites in animals (and sometimes directly in man) where stimulation and excision suggest localization of function.

From the anatomical background Dr. Fulton proceeds to behaviour studies made in animals before and after lesions in the regions concerned, and points out that the changes in behaviour are such as to support the views on the neural pathways for emotion derived from anatomical and physiological evidence.

In a final chapter he considers the evidence given by changes after operations on the frontal lobes in man. Here it is apparent that the author moves in a less familiar field, and it is not clear that he fully realizes how unreliable evidence from such material must perforce be. Nevertheless, he reviews carefully much of the diverse material available, and mentions especially those observations where attempts at limited lesions have been made. " Observation without hypothesis is valueless ", and Dr. Fulton certainly brings hypothesis, derived from experimental studies, to the formulation of observations made on man. The result is refreshing, even if it makes the problems seem simpler than they really are.

Brain Metabolism and Cerebral Disorders. By H. E. Himwich. (Pp. 452 ; 52 figures. 46*s*. 6*d*.) London : Baillière, Tindall & Cox. 1952.

This book is divided into two parts. In the first, labelled " energetics ", the various metabolic systems of the brain are reviewed. The evidence that carbohydrates are the main source of brain " energy " is detailed, and some protective devices are described by which this organ's supply of nourishment is maintained when the general supply becomes low. Studies of transmission of nerve impulses both in axons and across synapses, whose accompanying ionic changes represent considerable expenditure of electrical energy, emphasize that the brain must have fairly high energy requirements for its efficient functioning. The finding quoted in this book that something like 20% of the total oxygen consumption of the resting individual is used by the brain is therefore not entirely surprising. Consideration is given to changes in this consumption in various disease processes. The results are not always what might be expected *a priori*, though there is a tendency for reduction to be correlated with physical reduction of brain function rather than lessened " mental" activity. It will be interesting to know, however, whether the reduction found after lobotomy—apparently even in that part of the brain behind the cut—is confirmed, as such a change might be correlated with the reduction of drive so often seen post-operatively.

In the second part the patterns of nervous activity revealed both in the somatic and autonomic nervous systems by hypoglycaemia and anoxia are considered.

The suggestion is made that such studies confirm for both systems the existence of segregable "levels" in the Jacksonian sense.

The book contains much useful biochemical information, but is loaded also with many passing references to clinical facts which are sometimes of doubtful validity and relevance. As a source of biochemical reference it will be of value to the clinician who has no time or opportunity for seeking the original works. The whole subject is of such undoubted importance to the clinician that good interpreters are certainly required in this field.

Cell Growth and Cell Function. By T. O. Caspersson. (Pp. 185; 94 figures. 28*s*.) London: Chapman & Hall. 1950.

This book is based on T. W. Salmon memorial lectures, delivered by Prof. Caspersson in the U.S.A. It describes extensive studies on cell structure made at the Karolinska Institute in Stockholm. The work is based on ultra-violet microspectrophotometry, which has been developed to a high standard in recent years.

The first 60 pages give a very clear and readable account of the technique used, and of many of the precautions needed to get reliable results in this difficult field. There follows a short section on the microspectrography of nucleotides and proteins, and then studies of protein metabolism during the mitotic cycle. Later chapters describe studies of cytoplasmic protein formation in the normal cell, and in some tumour cells and viruses. The illustrations are clear and well chosen, and include many photomicrographs showing the effect of different treatments on cell structure.

While the book is primarily of interest to specialists in cytology or biochemistry, it is not without interest to neurologists. Thus, Figs. 66 and 67 show the striking decrease in cytoplasmic protein masses, and in nucleotides, which are produced in the anterior horn cells of guinea-pigs by heavy muscular work. Similar changes are shown in cochlear cells following acoustic stimulation. The work thus shows clearly the rapid formation and destruction of protein which occurs in nerve cells after vigorous stimulation, a point of great interest in connexion with paralytic poliomyelitis. In later chapters illustrations of nerve cells in different stages of infection with poliomyelitis and other viruses are also of clinical interest.

Die Darstellung von Lymphstromungen im inneren Milieu des Gehirns mit Hilfe der Ausbreitung von Bakterien bei entzündlichen Hirnkrankheiten. By R. A. Pfeifer. (Pp. 92; 73 figures. DM. 10.–.) Leipzig: Akademische Verlagsgesellschaft Geest & Portig K.-G. 1951.

This book describes studies of the distribution of *Spirochaeta pallida* in post-mortem sections of the brains of patients with general paralysis, and the relation of this distribution to the course and type of blood vessels in different parts of the brain. The work thus continues Prof. Pfeifer's earlier work on "Kreislauf und Hirntuberkulose" published in 1935, in which studies were made with brains invaded by *Myco. tuberculosis*.

The author's studies of blood vessels lead him to believe in the hypothesis first put forward by Sepp, that in the brain the exchange of fluid between blood vessels and tissues occurs chiefly along the arterioles (pre-capillaries) and venules (post-capillaries), while the exchange of gases occurs chiefly through the walls of the capillaries. In support of this view the author mentions the aerophilic tendency of the granular cells in the sensory region and the serophilic tendency of the pyramidal cells in the motor region with a corresponding prevalence of long pre-capillaries in the motor region and short ones in other zones.

The distribution of blood vessels in the cerebellum is then described, and it is concluded that since the arterioles and venules of the molecular layer run parallel to each other, a lymph flow parallel to the surface is to be expected in this region. Illustrations are shown of spirochaetes spread out roughly parallel to each other, like a school of fish, as might be expected in a lymph stream of this type. (Presumably only if the rear end of each organism became anchored to some fixed cell?) Other illustrations from sections taken perpendicular to the surface show numerous spirochaetes as seen end-on, i.e. perpendicular to the plane of the section.

Later sections of the book discuss the more complex distributions of blood vessels and spirochaetes found in the cerebrum, and their distribution in perivascular spaces. Findings with certain atypical cases of paralysis then follow.

Seventy-three illustrations, nearly all from microphotographs of brain sections, show various patterns of distribution of blood vessels and spirochaetes in the brain. A few of them show a strikingly regular distribution of spirochaetes, and many of them are quoted as evidence in favour of the author's view that the distribution of parasitic organisms in the brain is determined primarily by the lymph flow in various parts, and can therefore be used as an indicator of this flow.

However, no statistical evidence is provided to show how far the more regular distribution of organisms occurs constantly and widely in the areas where the "angioarchitectonic" structure is suitable, or how far the examples showing regularity are isolated instances found among large numbers of irregular patterns. From the exceptions mentioned on pp. 67–68 it is clear that the author has considered this question. However, further quantitative evidence on this point would add much to the value of the work.

Hirnatrophische Prozesse im mittleren Lebensalter und ihre psychisen Erscheinungsbilder. By F. W. Bronisch. (Pp. 105; 43 illustrations. DM. 12.60.) Stuttgart: Georg Thieme. 1951.

This monograph is devoted to a group of patients, who have generalized cerebral atrophy as shown by air encephalograms. All 14 patients presented as psychiatric cases, although various neurological symptoms and signs were present. Histological examination

of the brain, which was performed in five cases, showed various aetiological conditions; but the pathology of the other nine cases remains unknown.

The Abnormal Pneumoencephalogram. By Leo M. Davidoff and Bernard S. Epstein. (Pp. 506; illustrated. 105*s*.) London: Henry Kimpton. 1950.

This volume is a companion to "The Normal Encephalogram" by Davidoff and Dyke, a work now in its third edition and recognized as an authoritative account of the subject. The scope of "The Abnormal Pneumoencephalogram" is not confined to descriptions of radiological appearances, but includes short accounts of various conditions from a clinical and pathological aspect; a large number of illustrative case histories is also given. This increases the value of the book to those whose work does not bring them into everyday contact with clinical neurology. Films obtained by ventriculography and encephalography are described, but details of technique are not mentioned as these are to be found in the earlier work.

The first section is devoted to the appearances found in association with tumours, which are described according to their situation. Non-neoplastic conditions are dealt with in the second part, including some relatively uncommon examples, such as agenesis of the corpus callosum, which have been specially studied by the authors. The majority of chapters begin with an introduction and a review of the relevant literature. It may be found that the detailed descriptions of the authors' material which follow, although of value in an exhaustive study of the subject, make difficult reading and might confuse anyone trying to master the elements of pneumoencephalography. However, this difficulty is admirably overcome by the inclusion, in most chapters, of a comprehensive summary crystallizing the information and giving the conclusions to be drawn from the material described. There are usually a few final paragraphs on differential diagnosis.

The illustrations in a work of this kind are as important as the text, and on the whole they are of high quality. However, some of the radiographs have suffered in reproduction, and in a few of the figures the points described in the legends are by no means clear.

This book cannot fail to be of great assistance to those concerned with neurological diagnosis. It is a valuable survey of a large amount of material, and as a guide to the literature of the subject it will be found to be useful as a work of reference.

Unravelling Juvenile Delinquency. By Sheldon and Eleanor Glueck. (Pp. 399; 40*s*.) London: Geoffrey Cumberlege. 1950.

This is one of the very few books in which an investigation into juvenile delinquency has been conducted on a satisfactory design and with control material. The subjects were collected from boys admitted to correctional schools, i.e. persistent offenders, the controls from the general school population, after ascertainment of freedom from a delinquent record. The two series were matched in ethnic origin, age, and intelligence. By dint of what must have been an enormous amount of spade-work 500 boys in each series were obtained. Social case work, psychological testing, and other techniques then provided the basic material for a statistical study.

With such an excellent design, the results of the research deserve serious attention. Statistically significant differences were found between the two groups in a large number of fields. In family background both groups were under-privileged, but the delinquents came from poorer homes, receiving more relief, and their parents were more frequently unmarried, separated, or divorced. The average family sizes were the same. In the families of the delinquents there were more mental retardation, emotional disturbances, drunkenness, and criminality. Standards of conduct in the families of the delinquents were generally lower, and family affection between parents and children much less. Despite their matched intelligences the delinquents were educationally more retarded and much more frequently disliked school. Spare-time activities showed more adventurousness in the delinquents, greater craving for excitement, and more frequent adherence to gangs. Careful physical and medical examinations did not show any poorer physical health in the delinquents; indeed, neurological and neurotic anomalies were more frequent in the controls, and the delinquents had the greater strength of hand-grip. There were well-marked differences in physical constitution, the delinquents being of greater bodily size, more broad-shouldered, more muscular, more masculine. Psychiatric examination and temperamental tests, e.g. the Rorschach, showed more assertiveness in the delinquents, more defiance, more resentment of authority, less susceptibility to the fear of failure and defeat, less conventionality, less dependence on others, less self-control, more impulsiveness, more inclination to the immediate indulgence of an appetite.

These findings are discussed from the points of view of predicting delinquency, the causes of delinquency, and the future outlook in treatment and research. The book closes with a number of bulky appendices giving the factual data in detail.

The importance of this book lies as much in the negative as in the positive findings, in the points in which there were no differences between delinquents and controls as much as in those where significant differences were found. Many plausible suppositions which have been raised from time to time have failed to find any support. The general hypothesis which seems to emerge with the greatest clarity is that we should not look for the main causes of delinquency in pathological factors, physical or psychological. The most basic cause may well lie at least as much in the present structure of society as in the individual. The present pattern of civilized culture is highly suitable for the passive individual, the conformer, and personalities of a more robust kind may tend towards delinquency merely because they have not been provided with adequate socially acceptable outlets.

BOOKS RECEIVED

(Review in a later issue is not precluded by notice here of books recently received.)

***Introduction to Clinical Neurology.** By Gordon Holmes. 2nd ed. (Pp. 197; illustrated. 12*s.* 6*d.*) Edinburgh: E. & S. Livingstone. 1952.

New Outlook on Mental Diseases. By F. A. Pickworth. (Pp. 304; illustrated. 60*s.*) Bristol: John Wright. 1952.

***The Diagnosis of Nervous Diseases.** By the late James Purves-Stewart and C. Worster-Drought. 10th ed. (Pp. 962; 388 illustrations. 50*s.*) London: Edward Arnold. 1952.

***A Synopsis of Neurology.** By W. F. Tissington Tatlow, J. A. Ardis, and J. A. R. Bickford. (Pp. 513; 84 illustrations. 30*s.* Bristol: John Wright. 1952.

Therapeutic Studies of Psychotics. By Julius I. Steinfeld. (Pp. 262; 12 tables, 1 diagram. No Price.) Des Plaines, Ill., U.S.A.: Forest Press Publishers. 1951.

***The Educability of Cerebral Palsied Children.** By M. I. Dunsdon. (Pp. 164; graphs and tables. 21*s.*) London: George Newnes. 1952.

Pratique Neurologique. By M. Riser. Vols. I and II. (Pp. 1,428; 374 illustrations. 10,000 francs.) Paris: Masson et Cie. 1952.

***A Textbook of Clinical Neurology.** (With an introduction to the history of neurology). By Israel S. Wechsler. (Pp. 801; illustrated. 47*s.* 6*d.*) London: W. B. Saunders. 1952.

General Theory of Neurosis. By Rudolf Brun. (Pp. 469; 3 diagrams, 3 colour plates. 70*s.*) London: George Allen and Unwin. 1951.

Die Grenzen der Psychotherapie. By G. Ewald. (Pp. 36. DM. 3.30.) Stuttgart: Georg Thieme. 1952.

***Textbook of Clinical Neurology.** By J. M. Nielsen. 3rd ed. revised and reset. (Pp. 709; 212 illustrations. 75*s.*) London: Cassel. 1951.

A History of Neurological Surgery. Edited by A. Earl Walker. (Pp. 583; 152 illustrations. 91*s.* 6*d.*) London: Baillière, Tindall and Cox. 1951.

***Frontal Lobotomy and Affective Behaviour.** By John F. Fulton. (Pp. 159; 20 figures. 21*s.*) London: Chapman and Hall. 1951.

Abnormal Psychology. (A revision of Edmund S. Conklin's "Principles of Abnormal Psychology".) By D. B. Klein. (Pp. 589; illustrated. 40*s.*) London: George Allen and Unwin. 1952.

Cerebral Mechanisms in Behaviour. The Hixon symposium. Edited by L. A. Jeffress. (Pp. 311; illustrated. 52*s.*) London: Chapman and Hall. 1951.

Über den Wahn. By Kurt Schneider. (Pp. 48. DM. 3.90.) Stuttgart: Georg Thieme. 1952.

Les Nerfs Craniens. Anatomie Schématique de l'Appareil Nerveux. By René-Marcel de Ribet. (Pp. 568; 271 figures. 3,500 francs.) Paris: G. Doin. 1952.

Expert Committee on Drugs Liable to Produce Addiction. Third report. (Pp. 14. 9*d.*) Geneva: World Health Organization. 1952.

Die Nachkommen geisterkranken Elternpaare. By Günther Elsässer. (Pp. 340; 38 diagrams. DM. 33.00.) Stuttgart: Georg Thieme. 1952.

* Reviewed in this issue.

THE FEBRUARY (1952) ISSUE

The February (1952) issue contains the following papers :—

Posterior Fossa Dermoid Cysts with Special Reference to Intracranial Infection. By Valentine Logue and Kenneth Till.

Cerebral Poliomyelitis in Early Infancy. By Victoria Smallpeice and Christopher Ounsted.

Neuropathies Caused by Bony Spurs in the Cervical Spine with Special Reference to Surgical Treatment. By K. Lewer Allen.

Tridione Compared with Malidone in the Treatment of Petit Mal. By A. J. M. Butter.

Cognitive Factors in Epilepsy. By Margaret Davies-Eysenck.

Herpes Zoster Ophthalmicus and Post-Herpetic Neuralgia. By W. F. T. Tatlow.

The Effect of Denervation on Nail Growth. By S. Sunderland and L. J. Ray.

Memory Defects after Head Injury. By Moyra Williams and O. L. Zangwill.

Pulse-wave Electrocoma. By E. B. Strauss, J. Gould, and Angus MacPhail.

Prolonged Compression of the Brain Resulting from an Extradural Haemorrhage. By G. F. Rowbotham and N. Whalley.

Abscess Formation in a Pituitary Adenoma. By Norman Whalley.

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 12s. 6d.